

*For Schizophrenia Bulletin*

## **Animal models of hallucinations observed through the modern lens: Commentary**

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The review by Waters and Fearneyhough<sup>1</sup> makes it clear that there is nothing especially distinctive about hallucinations in schizophrenia, not even to the extent of hallucinations in the auditory modality being more prevalent than in the visual one, or hallucinations in schizophrenia having a greater preponderance of angry, critical voices. Hallucinations may occur both in people without mental disturbances, and also as a consequence of many different pathologies, including tinnitus and Parkinson's disease and other neuropsychiatric disorders such as post-traumatic stress disorder. This conclusion is consistent with a Research Domain Criteria (RDoc) approach to psychiatric nosology, as hallucinations are evidently trans-diagnostic with respect to the categorical diagnosis of schizophrenia or psychosis. What does this mean for animal models of hallucinations and, more indirectly, for understanding neurobiological mechanisms underlying hallucinations? Is the task of modeling hallucinatory behavior in animals any more revealing or useful than it was some 50 years ago when there was a major drive to understand the effects of hallucinogenic drugs acting at serotonin (5-hydroxytryptamine, 5-HT) receptors, such as LSD<sup>2</sup>? This commentary will endeavor to address these issues in the context of recent neuroscientific advances.

Most definitions of hallucinations generally stress the uncoupling of subjective responses to external input. Such dissociations, which imply a loss of stimulus control or attention to *input*, are complementary in some ways to those of other disorders, such as obsessive-compulsive disorder, where there is a loss of experienced response control, or attention to *output*. The obvious fact that hallucinations in humans are generally defined in terms of subjective verbal

report immediately appears to impose difficulties for animal studies, as also for other disorders such as depression. However, to adopt a sceptical stance, the inference of hallucinations in humans often itself depends on less than reliable subjective reports rather than directly measurable overt behavior, whereas it is often possible to infer some correlate of subjective processing in experimental animals from their overt behavior. In other words, it may be feasible to bridge what initially seems to be an impossibly wide gap between animal and human sensory experience, especially if a neuroscientific approach is adopted to make functional links via the strategy of triangulation of common mechanisms.

Changes in overt behavior in animals in the apparent absence of changes in sensory input are not in general sufficiently convincing as evidence of hallucinations because the behavior could simply be generated spontaneously. For example, limb flicks in cats<sup>3</sup> or head twitches<sup>4</sup> or startle in rodents<sup>5</sup> or checking behaviors in monkeys<sup>6</sup> caused by drugs such as 5-HT<sub>2A</sub> or dopamine receptor agonists could simply arise from forms of motor disinhibition in descending output pathways. The fact that such simple behaviors are produced by drugs known to be hallucinogenic in humans and are predictive of hallucinogenic potency in humans is certainly relevant, although given that 5-HT receptors are so widely dispersed in brain regions specialised for sensory, associative and motor functions, makes the correlations less compelling.

But the occurrence of entire, coherent sequences of apparently goal-directed behavior occurring in the absence of sensory support or the goal itself makes the inference of hallucination much more convincing. For example, the influential model of amphetamine psychosis arising from chronic administration of amphetamine produces not only repetitive stereotyped movements and a progressive fragmentation of behavior, in rats<sup>7</sup>, cats<sup>8</sup> and non-human primates<sup>9</sup> but some examples of monkeys apparently attending to imaginary stimuli in space, retrieving the stimuli with a grasp, and then bringing the 'object' to the mouth and chewing them<sup>7</sup>. This would appear to be an excellent example of a behavioral 'hallucination'

and the literature has many other dramatic examples<sup>9</sup>. However, these demonstrations, impressive and fascinating as they are, have perhaps limited significance for drug discovery probably depend on many uncontrolled aspects of the animal's environment and previous experience and hence are not easily reproducible.

How can we make use of a more explicitly neuroscientific approach to improve our attempts to model hallucinations, especially in the wake of the exciting tools we have in the form of transgenic, optogenetic and chemogenetic manipulations, as well as multi-unit electrophysiological recording and enhanced cellular and neural network imaging techniques? Such manipulations can help better to understand the mechanisms at a neuronal level by which hallucinations occur – for example, by chemical dysmodulation of signal-to-noise efficiency in relevant regions of the cerebral cortex and the sensory-thalamocortical pathways. Thus the thalamic input to layer 4 in the sensory neocortex is rather selectively modulated by ascending 5-HT fibers from the dorsal raphe nucleus<sup>10</sup>. Already, successful attempts have been made with transgenic knock-out mice to dissect various pharmacological responses to 5-HT receptor agents, including those responses correlated with hallucinogenic potency. Gonzalez-Maeso et al<sup>11</sup> showed that by genetically expressing 5-HT<sub>2A</sub> receptors only in the mouse cortex these 5-HT regulated pathways on cortical neurons were sufficient to mediate the signaling pattern and behavioral response to hallucinogens. The causal impact of this relationship for cortical perceptual processing could thus be further probed during the behavioral effects of drugs such as 5-HT<sub>2A</sub> receptor agonists, with obvious implications for human hallucinations. Other approaches may focus on the balance of cortical glutamate and GABA functioning relevant to the dissociative effects of drugs such as ketamine and phencyclidine. They may be used to test hypotheses that hallucinations result from impairments of timing and oscillatory synchrony of neuronal firing<sup>12</sup> caused for example by loss of parvalbumin GABA inter-neurons<sup>13</sup>. What must thus be borne in mind is that neuromodulation could be deficient as a consequence of a number of different molecular changes, and so what appears as a common phenotype of aberrant perception might be caused

by a variety of different molecular pathologies. Hence, similarity of hallucinatory experience across disorders may reflect final common pathway mechanisms without implying or confirming similar causal pathophysiology.

The main limitation of such approaches may be in terms of homology of the relevant neural structures across species, especially given the obvious species differences in sensory capacity as a function of modality - this may be a strong argument for the use of non-human primates, better to facilitate investigations of aberrant visual and auditory processing. At a systems level, some hypotheses concerning hallucinations depend on failure of monitoring by which sensory stimulation is not adequately modulated by back-projections of the prefrontal cortex to achieve effective corollary discharge<sup>14</sup>. This type of theory clearly requires recording neuronal activity simultaneously across defined neural networks using multi-electrode assemblies in order to define the hypothesized disconnection syndromes. The necessary triangulation with human findings could be further provided by magnetic resonance neuroimaging in both species (and magnetoencephalography in humans), combined with magnetic resonance spectroscopy to measure cross-species e.g. GABA/glutamate ratios.

Some of the most powerful evidence in humans has been to show that subjective verbal reports of auditory hallucinations in the absence of external stimulation nevertheless can be accompanied by activations in primary and language areas of auditory cortex<sup>15</sup> (see also review<sup>16</sup>) or in more widely distributed (and probably disconnected) neocortical and hippocampal networks<sup>17</sup>. Clearly, if such anomalous neuronal activity, detected by arrays of tetrodes, in sensory regions of the cortex in the absence of external stimulation in experimental animals can be linked to performance of simple hallucinatory type behaviors, such as checking or orienting, or more complex reactions, then this is getting close in operational terms to what can be observed in humans. Similarly, optogenetic stimulation could be used to simulate 'artificial' sensory inputs in order to determine whether they elicit hallucinatory type behaviors. Recently, for example, it has been shown that a population of

cells in the dentate gyrus of the mouse hippocampus encoded a particular external sensory context, the engram of which could be reactivated optogenetically to generate a false memory<sup>18</sup>. This demonstration of ‘false memory’ shows that it may be possible to evoke internal neuronal activity that is then interpreted by the individual as real perceptual phenomena.

What may emerge from this neurobiological analysis, combined with novel theoretical approaches in neuropsychology and computational neuroscience, is a new way of classifying hallucinations that will enable commonalities across diagnostic categories and possible differences to be more readily identified. It seems likely that hallucinations can potentially arise from a variety of underlying causes and mechanisms and a first step would be to assess this possibility in a variety of models of schizophrenia (and perhaps other disorders) and determine how this maps onto possible clinical heterogeneity. If the RDoc approach is ultimately to be useful in psychiatry, in my view it will have to be able to advance novel mechanistic accounts of psychiatric symptoms such as hallucinations, and show how they can be manifested and treated effectively across a range of pathologies.

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