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COMMENTARY

Current Approaches to Studying Hallucinations: Overcoming Barriers to Progress

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Efforts to understand the biological basis of auditory verbal hallucinations (AVHs) have been hampered by a number of problems. First is the historic tendency to only study patients with schizophrenia, whose medication, social, cognitive, and economic status confound the assessment of this isolated symptom. Second is the dominant belief that AVHs in schizophrenia are qualitatively different from those experienced by people with other diagnoses. Third and fourth are difficulties assessing the phenomenology of AVHs, and then mapping phenomenology onto underlying psychological and neural constructs. Fifth is the difficulty of assaying the state of AVHs rather than the trait, or tendency to have AVH. In this commentary, I address each of these, and when appropriate, reference the RDoC framework, which may be helpful in studying the neurobiological basis of AVH.[1,2]

Waters and Fernyhough[3] address the first 2 barriers to progress. First, they show that AVH can be studied across the wellness spectrum; both schizophrenia and nonclinical populations perceive AVH similarly, in so far as they seem to originate in external space and speak in a running commentary, key features of AVH in schizophrenia. This opens up the possibility of using brain imaging methods to study AVH in nonclinical populations, unaffected by the sequelae of serious mental illness, as has already been done to a limited extent.[4]

Second, they show that patients with other psychiatric and neurological diagnoses describe a similar phenomenology as patients with schizophrenia. Psychiatric disorders include alcohol dependence disorder, cannabis abuse, tinnitus, dissociative identity disorder, PTSD, bipolar disorder, borderline personality disorder. Neurological disorders include temporal lobe epilepsy and narcolepsy. If AVH were an isolated symptom in these disorders, they could be studied in a somewhat purer form than in the schizophrenia population. However, AVH is not an isolated symptom, except perhaps in nonclinical groups reporting AVH.

The concept of "equi-finality" is relevant here,[5] and the framers of the RDoC framework may have had it in mind when they invited investigators to step back from diagnoses and focus on basic dimensions of functioning, across the wellness and disease spectrum. That is, if the symptom (eg, a running negative commentary) is the *same* ("equi-final") in 2 different clinical groups, but the diagnosis (eg, schizophrenia vs PTSD) and etiology (eg, genetics vs trauma) are different, can we assume the same proximal neurobiological mechanisms are involved[6] in the AVH experience? This could be addressed by using neurobiological measures sensitive to domains of dysfunction (eg, failures of self-monitoring or cognitive control) across groups. To assess differences in the more distal roots of the hallucinatory experience would require different methods, likely involving in-depth medical, trauma, and psychiatric histories.

The third hurdle to understanding the neurobiological basis of AVH is the difficulty we face in assessing the phenomenology of the experience. For a number of reasons, it is difficult to assess the quality, quantity, and content of AVH. For example, if patients are guarded, they may not want to discuss the voices they hear. Alternatively, there may be a tendency to over-endorse due to the demand characteristics inherent the symptom interview. Experienced patients will agree with the interviewer that they hear voices instead of describing the actual experience they feel, which is possibly more akin to a feeling that someone is trying to communicate with them or a to feeling of presence of another person than to hearing audible voices. It is important to keep in mind that when we ask patients to describe their voices, we are asking them to do a meta-cognitive task. It is like asking friends to describe the nature of their thoughts. "Are they just ideas? Are they words? Are they wisps of meaning? Do they have sentence structure?" Like us, patients may not have the right words in their lexicon to describe the inner experiences they are having.

Fourth, the phenomenology of AVH (however valid) suggests the involvement of several different psychological constructs with underlying neural mechanisms. AVH are often described as words, suggesting the involvement of language and brain areas supporting AVH. However, to the extent that AVH are like thoughts, they may or may not have linguistic qualities. Thoughts pop up spontaneously, are unbidden and difficult to control. This is the normal experience of all of us; as our minds wander, we encounter unbidden thoughts, conversations we just had or are planning to have, and we can often "hear" the tonal quality of the other person's voice. What converts this *normal* experience into a *hallucination* may be the sense that the experience is not self-generated. That is, regardless of content, tone, linguistic quality, or familiarity of our thoughts, these unbidden experiences have no sense of willed intent, nevertheless, we seem to have a sense that they are coming from ourselves, rather than from an external source. As said so eloquently by Gallagher,[7] "Not only do they appear to be part of my stream of consciousness, but, despite the fact that I am not willing them, and may even be resisting them, they still seem to be generated within my own cognitive experience."

Perhaps when the "sense of self" is out of balance, thoughts may be "heard," suggesting the involvement of the RDoC construct of "agency" and the associated concept of self-monitoring. Indeed, a failure to monitor inner (self) speech (thoughts) is a leading explanatory construct of AVH.[8] Relevant to the above discussion, both clinical and non-clinical groups with AVHs have difficulties in identifying their own actions and thoughts, and commonly misattribute self-generated behaviors to an external source.[9] Importantly, some people are able to distinguish between AVH in their own and other people's voices,[10] questioning whether failures of agency could be responsible for "self" AVHs.[11]

Although it is the dominant theory of AVH, self-monitoring failures do not explain all features of AVH. They do not explain how unconscious thoughts become conscious and salient, and have disturbing or disruptive content. The "engine" for these experiences may be a hyper-connectivity between cortex and the striatum, such that unconscious activity gains access to consciousness.[12] This network might be responsible for registration of sensory aspects of experience, including the acoustic vocal characteristics. The non-self perception of this experience may result from dysfunction in the self-monitoring mechanism.[13] These two aspects of the AVH experience suggest different mechanisms and different ways of studying them: Hyper-connectivity has been studied using connectivity analysis of fMRI data,[14,15] and failures of self-monitoring have been studied using both fMRI[16] and EEG.[17] Regarding the latter, the mechanisms involved in self-monitoring have been studied across the animal kingdom[18] and could ultimately serve as endophenotypes for AVH in animal models.[19]

Fifth, it could be argued that uncovering the neurobiological basis of AVH is best done using a "symptom capture" approach, a naturalistic approach where neurobiological data are collected as people experience a hallucination. While this approach is conceptually simple, it is difficult in practice because it relies not only on the timely occurrence of an illusive subjective experience, but also on the ability of the person to reliably report its initiation and completion. Nevertheless, it has been used successfully in both clinical and nonclinical populations.[4] Also, connectivity analyses of fMRI data collected during the experience of AVH have proved successful.[12] Nevertheless, the more common and simpler approach is to compare a group of people who have the trait to hallucinate to different group of people who do not. Whether this truly assays the phenomenon remains a question.

I have not addressed hallucinations in other modalities, mentioned by Waters and Fernyhough.[3] The literature suggests that 50% of people diagnosed with schizophrenia who report AVHs also report visual hallucinations.[20,21] Those reporting AVHs are also more likely to report olfactory and tactile hallucinations than those who do not endorse AHs. Visual hallucinations in the absence of AVHs are reported much less frequently in people diagnosed with schizophrenia-spectrum disorders. The hallucination nidus may start in the auditory/voice network but then spread to other modalities. Alternatively, an earlier common path may originate in hippocampus[22] and connect memories to the language system for AVHs and other systems for hallucinations in other modalities. Visual hallucinations have not been studied with methods used to assess agency, but have been studied using connectivity analyses of fMRI data.[22,23]

In this commentary, I have highlighted several barriers to studying the neurobiological basis of AVH and how to overcome them. As a field, we have largely restricted our studies of AVH to schizophrenia patients. This is problematic because schizophrenia is characterized by other symptoms, co-morbidities, and a long list of clinical and social sequelae of serious mental illness, confounding the simple study of AVH. To overcome this, I argued that we might be able to study AVH in a "purer" form, by studying clinical and nonclinical populations who report AVH that are similar to those experienced by schizophrenia patients.[3] If true, we would be on solid ground when extrapolating from one group to another. Unfortunately, phenomenology of inner experience is hard to describe, as our efforts to describe the contents of our own wandering minds attests. I suggest that convergent validity for extrapolating from one group to another would come from neurobiological assays of AVH showing a similar pattern of findings across different groups who endorse similar types of AVH. Ideally those neurobiological assays would involve methods and mechanisms that can be translated to nonhuman animal models.[19]

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