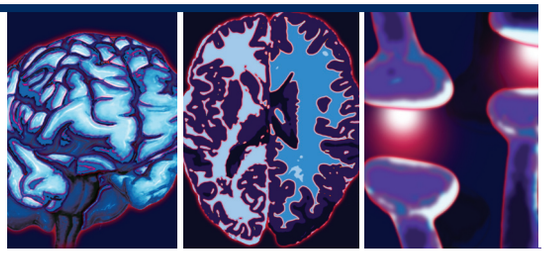
EDITORIAL



Hallucinations: find the networks

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"Chronic persistent hallucinations result in significant multilevel cognitive and social impairment with a severe impact on autonomy, skills and professional achievement and when worsening, generate auto- or hetero-aggressive behaviors."

Hallucinations, among the most fascinating but devastating manifestations of the mind, have attracted the interest of physicians and psychologists since the 19th century French psychiatrist Esquirol described visions and hearing voices as a unitary brain-related phenomenon (i.e., perceptions without object).

Hallucinations have been described in many psychiatric neurological or general conditions. More than 70% of patients suffering from schizophrenia are heavily affected by hallucinations during the course of the disease [1]. The recommended treatment is antipsychotic medication. However, for 25% of the patients with schizophrenia, hallucinations remain drug-resistant throughout their lives [2]. They usually describe hearing words, sentences through comments and conversations often intrusive. To a lesser degree they experience a false sense of presence or more complex phenomena such as elaborated, vivid, colorful or 3D hallucinations of humans or animals. Chronic persistent hallucinations result in significant multilevel cognitive and social impairment with a severe impact on autonomy, skills and professional achievement and when worsening, generate auto- or hetero-aggressive behaviors.

The development of brain imaging is intensively contributing to the further understanding of the neural basis involved in the mechanisms of hallucination in addressing morphometric, functional and connectivity issues in patients with schizophrenia. These findings have raised expectations for new therapeutic strategies like neuromodulation.

Hypotheses for the underlying mechanisms of auditory verbal hallucinations (AVH) have been proposed [3], most of which are not mutually exclusive. First, it has been proposed that AVH could result from aberrant perceptions generated in the auditory region. This has been suggested by the observation of the generation of involuntary auditory or verbal material during perioperative electrical stimulations of the temporal cortex in nonschizophrenic

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subjects [4]. External misattribution of self-inner speech has also been postulated to account for AVH. According to this model, patients with schizophrenia would be unable to identify their own thoughts as self-generated, instead considering them as intrusive alien voices within their heads [5]. Finally, dysfunctions in the neural substrates of episodic verbal memory have been proposed to account for the involuntary emergence of AVH [6]. Anatomical and functional disturbances in sensory cortices have been proposed to be centrally involved in their pathogenesis [7]. However, sensory pathway lesion models poorly explain the phasic course of hallucinatory episodes. In particular, lesion theories account for persistent symptoms but do not sufficiently explain how hallucinations, which are intermittent by nature, suddenly intrude into active thought.

Since the pathophysiology of hallucination is still poorly understood, neuromodulation strategies remain controversial and need to be validated. Several important issues furthering the understanding of these mechanisms are worth noting.

First, hallucinations are mainly explored in the auditory verbal domain. Although less frequent, hallucinations other than auditory are well documented in clinical observations. An exhaustive inquiry of hallucinations in the different sensory modalities accounts for 56% of complex visual hallucinations (VH) in this psychiatric disorder [8]. They are also frequent in young patients even during the earliest stage of the disorder [9]. To our knowledge, only few studies explored hallucinations independently of the underlying neuropsychiatric disorder by comparing different clinical populations with hallucinations. Moreover, there is increasing evidence that hallucinations in schizophrenia may arise from disturbances in distributed brain networks involving supramodal processing. Atypical functional connectivity in resting-state networks has been suggested in paranoid patients to account for the increased sensitivity to both the external environment and self-referential thought [10]. Furthermore, diffusion-weighting imaging studies revealed a greater white matter integrity, measured with fractional anisotropy (FA), in the arcuate fasciculus [11,12] in patients with AVH. Interestingly, FA in the inferior longitudinal fasciculus has been found to be smaller in patients with a history of VH compared with patients without VH [13]. Such opposite FA deviations suggest distinct pathophysiological mechanisms associated with verbal or VH. One limitation of this functional and anatomical research concerns the lack of generalization to the visual modality of hallucinations in schizophrenia.

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Second, the information provided by brain imaging studies depend on whether they are designed as 'trait' or 'state' studies. Most of the trait studies are cognitive studies comparing hallucinators with nonhallucinators to investigate the neural bases of the susceptibility to hallucinate, independently of the subjects' experience during scanning. These studies are unable to highlight mechanisms of the origin of the hallucinatory phenomenon. State studies are conducted during the occurrence of a hallucination, which allows the direct measurement of brain activations associated with symptom emergence. Only a few studies have been conducted in schizophrenia during the occurrence of auditory hallucinations, all reporting anatomical and functional disturbances in the auditory sensory cortices [14–17]. These studies are still nonexistent in the visual modality. The main reason is that 'capturing' the activity related to hallucinations is not simple. We have proposed an original approach based on independent component analysis validated in a preliminary study [18]. It has been argued that independent component analysis could be relevant in estimating functional statistical maps in case of unpredictable events, like a fluctuation of subject's performance or spontaneous cortical activities, such as hallucinatory episodes [19].

Another crucial limitation is the validation of a theoretical model able to integrate multiscale findings (at behavioral, cortical and network level). A computational approach should allow the combining of data regarding the susceptibility to hallucinate, even when the whole system is not involved in hallucinatory experiences at the time of testing, as well as neural structures recruited during hallucinations *per se*. In line with a recent review [20], it is crucial to test the assumption that disruptions in Bayesian inference could be responsible for the generation of hallucinations. This theory, initially proposed for auditory hallucinations, lacks experimental evidence in schizophrenia but also in other disorders in which hallucinations occur.

There is a need to integrate these complementary approaches and provide a transnosographic model for hallucinations. The exploration of

hallucinations of different sensory modalities in psychiatric and neurological disorder is a scientific challenge providing an opportunity to improve our understanding of the complex pathophysiological processes; a technological challenge by responding to the need for translational research combining behavioral, brain imaging and computational data; therapeutic challenge by improving detection of neural networks to improve neuromodulation strategies; and a social challenge by providing a clear explanation for a complex phenomenon and reduce stigmatization of patients suffering from hallucinations. Reducing stigma of patients would increase their social acceptance and improve the facilities for new patients to seek treatment.

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Bibliography

1 Andreasen NC, Flaum M. Schizophrenia: the characteristic symptoms. *Schizophr. Bull.* 17, 27–49 (1991).

2 Shergill SS, Murray RM, McGuire PK. Auditory hallucinations: a review of psychological treatments. *Schizophr. Res.* 32, 137–150 (1998).

3 Aleman A, Larøi F. *Hallucinations: The Science of Idiosyncratic Perception*. American Psychological Association, Washington, DC, USA (2008).

4 Penfield W. Some mechanisms of consciousness discovered during electrical stimulation of the brain. *Proc. Natl Acad. Sci. USA* 44, 51–66 (1958).

5 McGuire PK, Silbersweig DA, Wright I *et al.* Abnormal monitoring of inner speech: a physiological basis for auditory hallucinations. *Lancet* 346, 596–600 (1995).

6 Copolov DL, Seal ML, Maruff P *et al.* Cortical activation associated with the experience of auditory hallucinations and perception of human speech in schizophrenia: a PET correlation study. *Psychiatry Res.* 122, 139–152 (2003).

7 Jardri R, Pouchet A, Pins D, Thomas P. Cortical activations during auditory-verbal hallucinations: a coordinate-based meta-analysis. *Am. J. Psychiatry* 168(1), 73–81 (2011).

8 Bracha HS, Wolkowitz OM, Lohr JB, Karson CN, Bigelow LB. High prevalence of visual hallucinations in research subjects with chronic schizophrenia. *Am. J. Psychiatry* 146(4), 526–528 (1989).

9 Jardri R, Lucas B, Delevoye-Turrell Y *et al.* An 11-year-old boy with drug-resistant schizophrenia treated with temporo-parietal rTMS. *Mol. Psychiatry* 12(4), 320 (2007).

10 Zhou Y, Liang M, Tian L *et al.* Functional disintegration in paranoid schizophrenia using resting-state fMRI. *Schizophr. Res.* 97(1–3), 194–205 (2007).

11 Hubl D, Koenig T, Strik W *et al.* Pathways that make voices: white matter changes in auditory hallucinations. *Arch. Gen. Psychiatry* 61, 658–668 (2004).

12 Shergill SS, Kanaan RA, Chitnis XA *et al.* A diffusion tensor imaging study of fasciculi in schizophrenia. *Am. J. Psychiatry* 164, 467–473 (2007).

13 Ashtari M, Cottone J, Ardekani BA *et al.* Disruption of white matter integrity in the inferior longitudinal fasciculus in adolescents with schizophrenia as revealed by fiber tractography. *Arch. Gen. Psychiatry* 64(11), 1270–1280 (2007).

14 Dierks T, Linden DE, Jandl M *et al.* Activation of Heschl's gyrus during auditory hallucinations. *Neuron* 22(3), 615–621 (1999).

15 Jardri R, Delevoye-Turrell Y, Lucas B *et al.* Clinical practice of rTMS reveals a functional dissociation between agency and hallucinations in schizophrenia. *Neuropsychologia* 47(1), 132–138 (2009).

16 Shergill SS, Brammer MJ, Williams SC, Murray RM, McGuire PK. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Arch. Gen. Psychiatry* 57(11), 1033–1038 (2000).

17 Sommer IE, Diederen KM, Blom JD *et al.* Auditory verbal hallucinations predominantly activate the right inferior frontal area. *Brain* 131(Pt 12), 3169–3177 (2008).

18 Jardri R, Pins D, Bubrovszky M. Neural functional organization of hallucinations in schizophrenia: multisensory dissolution of pathological emergence in consciousness. *Conscious Cogn.* 18(2), 449–457 (2009).

19 van de Ven VG, Formisano E, Roder CH *et al.* The spatiotemporal pattern of auditory cortical responses during verbal hallucinations. *Neuroimage* 27(3), 644–655 (2005).

20 Fletcher PC, Frith CD. Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. *Nat. Rev. Neurosci.* 10(1), 48–58 (2009).