

# On the neurobiology of hallucinations

Patricia Boksa, PhD

Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montréal, Que.

Hallucinations are perceptions in the absence of an external stimulus and are accompanied by a compelling sense of their reality. They are a diagnostic feature of schizophrenia, occurring in an estimated 60%–70% of people with this disorder, with auditory hallucinations being the most common. However, hallucinations are not only associated with illness but can also occur in healthy individuals. For example, data from 6 community survey studies in various countries indicate that 7%–30% of children and adolescents report experiencing hallucinations.<sup>1</sup> In the context of grief after the death of a spouse, one-third to one-half of bereaved spouses report hallucinations of the deceased.<sup>2,3</sup> Transcultural influences may also affect the distinction between reality and imagination as well as the normalcy of visualizing images and ideas.<sup>4</sup> In healthy people, pseudohallucinations can even be generated at will by mild sensory deprivation; for example, vivid dreamlike visual imagery can be induced in some individuals by placing 2 halves of a ping pong ball over the eyes and playing a recording of the sounds of a waterfall for several minutes.<sup>5</sup> The neurobiological basis of hallucinations has most frequently been investigated in patients with schizophrenia, although studies examining hallucinatory phenomena in healthy individuals may also be informative. It should be noted, however, that it is unknown at present whether hallucinations are generated by similar mechanisms in patients and in healthy people.

How close are we to understanding the brain mechanisms responsible for hallucinations in psychotic disorders like schizophrenia? Among the various complex symptoms of psychotic disorders, it would seem that hallucinations might be a relatively discrete and precisely defined symptom, and therefore amenable to understanding the brain mechanisms involved. As a first approach to studying the mechanism of hallucinations, psychologically normal individuals with hallucinations due to lesions have been studied, and the lesion was generally found to be in the brain pathway of the sensory modality (e.g., auditory, visual, somatic) of the hallucination.<sup>6</sup> For example, the complex visual hallucinations seen in Charles Bonnet syndrome are most often caused by damage to the visual system such as macular degeneration or lesions

to the central nervous system pathway between the eye and the visual cortex.<sup>7</sup>

Recently, neuroimaging technology has been used quite extensively in an attempt to understand the brain regions and circuitry involved in the generation of hallucinations. Patients with schizophrenia experiencing auditory hallucinations have been studied most often. It might be expected that the basis for auditory hallucinations would be found in the brain regions known to subserve normal audition, language perception and language production. To briefly summarize these, the primary auditory cortex, which is involved with the perception of pure tone and pitch, is located on the dorsal surface of the superior temporal gyrus. This is surrounded by secondary auditory association areas that are involved in identifying more complex auditory sequences like the phonetic features of speech (but not its meaning). The middle temporal gyrus also contains association cortex responding to understandable speech. The 2 main language epicentres are the Wernicke area located in the posterior temporal and parietal cortex, which connects word meanings with objects and concepts, and the Broca area located in the inferior frontal gyrus, which is involved in sentence production. In addition, the anterior cingulate cortex, implicated in affect and attention, is thought to be involved in providing behavioural drive to produce speech, whereas the dorsolateral prefrontal cortex may provide a sense of the voluntary versus involuntary nature of auditory awareness.

Allen and colleagues<sup>8</sup> have recently provided an excellent comprehensive review of neuroimaging findings on “the hallucinating brain.” Hallucinations in patients with schizophrenia have been studied with respect to changes in central nervous system structure, function and connectivity. The most consistent finding of structural neuroimaging studies of patients with auditory hallucinations is reduced grey matter volume in the superior temporal gyrus, including the primary auditory cortex. One fairly large study also reported volume reduction in the dorsolateral prefrontal cortex, suggesting that faulty frontotemporal interactions may contribute to the experience of hallucinations being involuntary. Functional activation studies of actively hallucinating

Correspondence to: Dr. P. Boksa, Douglas Institute — Research, Pavilion Perry, Rm. E-2110, 6875 LaSalle Blvd., Verdun QC H4H 1R3; fax 514 762-3034; patricia.boksa@mcgill.ca

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participants have generally reported increased activity in language areas and in the primary auditory cortex, strongly implicating the superior and middle temporal gyri, although various other nonsensory cortical and subcortical areas have also been implicated. Several studies examining neural connectivity using diffusion tensor imaging or functional magnetic resonance imaging in patients with schizophrenia who experience auditory hallucinations have concurred in showing altered connectivity among temporal, prefrontal and anterior cingulate regions.

One major concept on the origin of hallucinations is the idea that hallucinating individuals may misattribute internally generated speech (or sensory stimuli) as coming from an external source.<sup>9</sup> Interestingly, Blakemore and colleagues<sup>10</sup> suggested that looking at why you can't tickle yourself may provide a window on this phenomenon. They propose that our experience of a self-generated tactile or other stimulus (e.g., tickling yourself) is attenuated compared with an externally generated stimulus (e.g., being tickled by someone else) because we anticipate the sensory consequences of a self-generated stimulus. They showed that healthy controls experienced self-tickling as less intense or tickly than tactile stimulation by an experimenter. In contrast, participants with auditory hallucinations or passivity phenomena (i.e., loss of the sense of boundary between self and others) did not discriminate between the 2 types of stimuli. The underlying mechanisms for such misattribution of self-generated acts are not yet understood. It has been hypothesized that such deficits in self-monitoring arise from a lack of connectivity between brain regions that initiate an act and regions that perceive the sensory consequences of the act (i.e., a failure of corollary discharge mechanisms).<sup>11</sup> In support of this concept, several studies have found evidence for reduced functional frontotemporal connectivity in patients with schizophrenia who were asked to speak or complete sentences, and this was particularly pronounced in those with auditory hallucinations.<sup>12,13</sup> Blakemore and colleagues<sup>14</sup> have provided experimental evidence that another required element enabling one to discriminate between self-produced and external stimuli is the correct placement of sensory stimuli in space and time. Recent studies have indicated that individuals with schizophrenia, particularly those exhibiting passivity symptoms, show deficits in judging time intervals, and it is hypothesized that this may contribute to dysregulated temporal coordination of information.<sup>15,16</sup> A deeper understanding at a neurobiological level of how we differentiate self from other is clearly relevant to the understanding of hallucinations, and insight into the neurobiology of timing may also prove relevant.

Another interesting approach that has been used to study hallucinations is the use of hypnosis to suggest hallucinations in healthy individuals. Szechtman and colleagues<sup>17</sup> reported that the right anterior cingulate cortex was activated in hypnotizable people when they heard real external speech or when they were instructed to hallucinate under hypnosis, but not when they imagined speech. They thus suggested that the anterior cingulate cortex may be involved in attributing the speech to an external source. As pointed out by Allen and colleagues,<sup>8</sup> however, controls (who were unable to hallucinate

under hypnosis) in this study should also have been expected to activate the anterior cingulate cortex when they heard real speech, but they did not. Interestingly Raz and colleagues<sup>18</sup> have demonstrated altered activation of the anterior cingulate cortex in highly hypnotizable people responding to a hypnotic suggestion (not involving hallucinations). This raises the possibility that the anterior cingulate cortex could be involved in hypnotic suggestibility per se (or in attributing control to an external source, possibly the hypnotizer) and illustrates the complexity of interpretation of these types of models. Another normal state that has been suggested to provide potential insight into hallucinations is rapid eye movement (REM) sleep, since hallucinations and delusions are regular features of REM.<sup>19</sup> For example, Blagrove and colleagues<sup>20</sup> reported that on waking from dreams during REM sleep, women (but not men) showed a deficit in monitoring self-generated versus externally generated stimuli.

In summarizing current knowledge on neuroimaging of hallucinations, Allen and colleagues<sup>8</sup> have proposed a model for auditory hallucinations in which there is overactivity in the primary and/or secondary auditory cortices in the superior temporal gyrus and altered connectivity with language processing areas in the inferior frontal cortex. The model also includes weakened control of these systems by anterior cingulate, prefrontal, premotor and cerebellar cortices. Basically, it appears that neuroimaging data have confirmed the expectation that hallucinations involve altered activity in the neural circuitry known to be involved in normal audition and language and their control. However, the major question of how this altered activity arises is still unanswered. Behrendt<sup>21</sup> has provided a thought-provoking hypothesis based on the idea that perceptual experience arises from synchronization of gamma oscillations in thalamocortical networks. This oscillatory activity is normally constrained by sensory input and also by prefrontal and limbic attentional mechanisms. There is evidence that in patients with schizophrenia there is impaired modulation of thalamocortical gamma activity by external sensory input, allowing attentional mechanisms to play a preponderant role in the absence of sensory input. This may lead to hallucinations. Moreover, conditions of stress/hyperarousal and neurochemical alterations characteristic of schizophrenia (e.g., nicotinic receptor abnormalities, dopaminergic hyperactivity) may be factors that predispose toward this uncoupling of sensory input from thalamocortical activity and pathological activation of thalamocortical circuits by attentional mechanisms. Thus, advances in understanding the modulation of gamma rhythms and their role in information processing may be particularly pertinent to understanding the neurobiology of hallucinations and other symptoms of schizophrenia. Recent elegant work establishing a critical role for interneurons containing parvalbumin (known to be reduced in schizophrenia) in generating gamma oscillations<sup>22,23</sup> provides examples of how basic neuroscience studies in experimental animals are contributing to this field.

With respect to treatment to lessen hallucinations, neuroimaging findings have provided information necessary to decide which brain regions might be targeted for trials of

repetitive transcranial magnetic stimulation (rTMS) to reduce auditory hallucinations. In these trials, slow rTMS was given over the right temporoparietal cortex in patients with schizophrenia experiencing treatment-resistant auditory hallucinations. Slow rTMS was used because it reduces brain excitability as opposed to the faster rTMS used to increase brain excitability in the treatment of depression. A recent meta-analysis<sup>24</sup> of these studies showed that rTMS significantly reduced auditory hallucinations with a mean effect size of 0.76. For comparison, the authors point out that a meta-analysis of the effects of clozapine versus typical antipsychotics in patients with treatment-resistant schizophrenia showed a mean effect size of 0.48, using total score on the Brief Psychiatric Rating Scale<sup>25</sup> as the outcome (although this latter meta-analysis did not aim to study hallucinations specifically). Thus rTMS may be a potentially efficacious treatment alternative for treatment-resistant auditory hallucinations.

Overall, the literature reflects the perplexing challenges inherent in investigating a higher mental process like a hallucination. In studies with human participants, neural processes can only be shown to correlate with, not to definitively cause, hallucinations. Animal models have often been used to provide evidence for causation. Behavioural observation would suggest that animals like monkeys and dogs have the ability to discern whether vocalization arises from themselves or from other animals. Thus one could anticipate that under abnormal conditions they might mistake internally generated representations of sounds as coming from another animal. However, behaviourally assessing the possible presence of such "hallucinations" in an animal is problematic. In studies in which monkeys are given drugs known to produce psychosis in humans, behavioural changes have been observed.<sup>26,27</sup> However, changes that have been categorized as hallucinatory-like behaviour (e.g., responses to nonapparent stimuli, staring for extended periods) are too nonspecific for research targeting mechanisms of hallucinations.

In conclusion, although useful insight has been gained, we still have a long way to go to fully understand what causes the "voices" and "visions" of schizophrenia. It is hoped that this brief editorial foray into the topic will provoke increased interest and thought on this fascinating and challenging subject.

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