Left with the voices or hearing right? Lateralization of auditory verbal hallucinations in schizophrenia

In an important contribution to the literature on the neural basis of hallucinations, Ait Bentaleb et al[1] describe, in a patient with schizophrenia, more metabolic activity in the left primary auditory cortex and the right middle temporal gyrus during auditory hallucinations than while listening to external speech. The authors conclude this finding indicates that the hypotheses of defective internal monitoring and of aberrant auditory activation are not mutually exclusive. In addition, however, their finding raises the question of whether hallucinations might be associated with aberrant lateralization of language function.

The finding of decreased cerebral asymmetry in schizophrenia has been replicated with several techniques.[2] In addition, functional imaging studies have reported decreased lateralization of language-related activation in patients with schizophrenia compared with healthy controls.[3] It could be hypothesized that inner speech, originating from right cerebral homologues of the language areas, is perceived as auditory hallucinations. Self-produced language activity normally leads to inhibition of language perception areas.[4] When this inhibitory mechanism is failing, verbal thoughts may not be recognized as originating from the self and may erroneously be attributed to an external source. Indeed, inhibition of language perception might be more prone to failure when language activity is derived from an unusual site (i.e., from contralateral homologue areas in the right hemisphere). This hypothesis can be tested by reviewing studies meta-analytically that report functional activation in patients with schizophrenia while they are experiencing hallucinations.

The following inclusion criteria were used: bilateral measurement of functional activity, right-handed patients with a diagnosis of schizophrenia, hallucination-related activity measured either in a block design or with event-related functional magnetic resonance imaging protocols.

Because we are interested in laterality of the verbal component of auditory hallucinations, our analysis was restricted to activity in areas that are known to be involved in language (i.e., Brodmann areas 21, 22, 38, 39, 40, 41, 42, 44, 45 and 52).

Significant hallucination-related activity was statistically integrated and compared among areas in the left and the right hemisphere using the logaritmic risk ratio method. To be less dependent on statistical thresholds of individual studies, data were also analyzed with a vote-counting method, which compares the number of language-related areas that are significantly activated in the right and left hemisphere.

Five studies met our inclusion criteria (Table 1), but only 3 could be included in the risk ratio analysis (Lennox et al,[6] Dierks et al[8] and Shergill et al[9]) because one study[5] provided insufficient data and the other[7] did not report activity in language-related areas. The resulting mean, weighted risk ratio (left/right) was 3.42 (95% confidence interval 2.89–4.81; $\kappa = 3$; total $n = 11$), implying stronger activity of left hemisphere language areas. All 5 studies were included in the vote-counting analysis, which also demonstrated that more left hemisphere ($n = 14$) than right hemisphere ($n = 7$) language-related brain areas were significantly activated during auditory verbal hallucinations.

Using 2 different methods, our results showed that language-related areas in the left hemisphere were significantly more activated than the right-sided homotope regions. Thus, the hypothesis that auditory verbal hallucinations arise from a right hemisphere source of language production (inner speech) and are subsequently perceived as originating from an external source is not supported by the available evidence. Instead, these findings call for a more thorough investi-

Table 1: Studies reporting functional cerebral activation in patients with schizophrenia during hallucinations

Study	No. of patients	Activated hemisphere	
		Left	Right
Woodruff et al[5]	1	0	2
Lennox et al[6]	4	3	0
Silbersweig et al[7]	5	0	0
Dierks et al[8]	2	7	1
Shergill et al[9]	5	4	4

gation of auditory verbal imagery and language perception in relation to hallucinations.

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The authors respond:

We would like to thank Sommer and colleagues for their comments regarding our article and for their meta-analysis of research into the lateralization of verbal hallucinations.[1] However, we believe that it is difficult on the basis of a meta-analysis alone to settle, once and for all, the issue of the lateralization of hallucinations.

First, 2 types of experimental paradigms have proved instructive regarding cerebral functions affected by schizophrenic hallucinations: (1) those where cerebral activity in the presence of a specific hallucination is compared with the activity that occurs in its absence; and (2) those where the cerebral activity that occurs during the performance of a specific task involving lexical or auditory data processing is compared with the activity that occurs when the participant is in a defined controlled state that clearly differs from the state under study. In each of these paradigms, if we wish to arrive at a sound interpretation of the data, measures must be taken to control the numerous sources of fluctuations in cerebral activity that could easily skew matters. Consequently, the studies to date have necessarily been heterogeneous, thereby complicating any meta-analysis.

Second, reviewing the conclusions drawn in functional imaging studies, we notice that anomalies have been observed in several regions of the brain, but there is no evidence of the worsening of a function located consistently in one or other of these. The problem appears to stem rather from an abnormal coordination of brain activation in various sites. In other words, we should be focusing more on connectivity than on lateralization.

Third, it seems conceivable that certain functional connectivity anomalies in the cortical regions could serve as relatively stable features capable of characterizing the disease, whereas others are transitory phenomena characteristic of a particular state. In this regard, certain observations suggest that during the acute stage of the illness, a generalized deficit occurs in the functioning of the 2 hemispheres, but particularly in the right. After remission, however, disturbances persist only in the left.[2] Any meta-analysis must take this into account.

Finally, it is useful to refer to a theory of language such as access to the mental lexicon (contribution of the left hemisphere), which calls for experimental paradigms such as those used for lexical decisions. The 2 hypotheses currently most studied to explain the genesis of auditory hallucinations are (1) an internal discourse not recognized as his own by the hallucinating subject and (2) aberrant activity accessing the primary auditory area. In most cases, the verbal content of auditory hallucinations remains the same from 1 psychotic episode to the next, even when the 2 episodes are separated by a long period of remission. This has led us to hypothesize that the verbal content of auditory hallucinations persists at a subclinical level even during periods of full remission and is quickly reactivated when the subject is exposed to stressful events. We also suggest that these 2 hypotheses apply above all to this specific verbal content.

To test these assumptions, we

used a lexical decision task with 12 right-handed adults (6 patients and 6 controls). The patients (3 men and 3 women) suffered from paranoid schizophrenia as per the DSM-IV criteria but had been well stabilized for at least 6 months. All had a history of auditory hallucinations, with at least 2 acute psychotic episodes of schizophrenia during which they presented the same verbal hallucinatory content. Moreover, at the time of the study, patients had not experienced a hallucination for at least 6 months.

The controls (3 men and 3 women) were matched to the patients. Two lists of words (H and A) and 2 lists of non-words (NH and NA) were used with each patient–control pair. The H list consisted of words from the verbal content hallucinated by a given patient during at least 2 psychotic episodes separated by at least 6 months' remission. The A list was made up of words matched with those of the H list on the basis of length, semantic content, affective valence, abstract–concrete dimension and frequency of use, as per the word frequency dictionary by Jean Beaudot.[3] The stimuli (i.e., words from the H, A, NH and NA lists) were constructed on the basis of the hallucinatory content of a given patient (H list). They were used with the patient in question and his/her control alone. In other words, we constructed 6 groups of stimuli, each group being specific to a patient–control pair.

The stimuli were represented by black characters (Geneva 44 font) on a white background. They were presented on a computer screen and remained there until the subject responded. Once a response was given, the second stimulus appeared on the screen after a delay of 499 ms. The stimuli were presented in random order except that no more than 3 stimuli from the same list could be presented in a row, as has been the practice in most lexical decision studies. Before beginning, the subjects underwent brief training with non-experimental lists to familiarize themselves with the task. They were told to press the right arrow of the computer keyboard if they recognized the word and the left arrow if they did not (i.e., if the word was not part of their vocabulary).

The mean word-recognition error rate for the controls was 2.75% and never exceeded 5%, and for the patients it was 13.3%. For 2 of the 6 patients, the rate was less than 5%, but the other 4 presented a mean of 19.3%. It was interesting to note that 78% of the errors committed involved non-words mistaken for real ones. Most of the non-words converted into words by the subjects with a history of hallucinations came from the NH list (83% v. 17% from the NA list). The results also showed that the subjects with a history of verbal auditory hallucinations were slower than controls in recognizing all words, regardless of the list they belonged to. The median time required for patients to recognize a word was 1048.66 ms, and for controls, the time required was 679.91 ms ($p = 0.004$). Finally, the patients were significantly faster ($p \leq 0.001$) at recognizing the words from the H list than those from the A list (median time 823.25 ms for H list v. 943 ms for A list). Among controls, there was no significant difference between the amount of time required to recognize words from either list.

These results indicate that even during periods of full remission, patients are quicker to recognize words that are part of their hallucinations than those that are not. This corroborates the idea of a lexicon specific to hallucinated words that undergoes special cognitive processing by subjects during high-stress episodes.

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