Mapping Auditory Hallucinations in Schizophrenia Using Functional Magnetic Resonance Imaging

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Background: Perceptions of speech in the absence of an auditory stimulus (auditory verbal hallucinations) are a cardinal feature of schizophrenia. Functional neuroimaging provides a powerful means of measuring neural activity during auditory hallucinations, but the results from previous studies have been inconsistent. This may reflect the acquisition of small numbers of images in each subject and the confounding effects of patients actively signaling when hallucinations occur.

Methods: We examined 6 patients with schizophrenia who were experiencing frequent auditory hallucinations, using a novel functional magnetic resonance imaging method that permitted the measurement of spontaneous neural activity without requiring subjects to signal when hallucinations occurred. Approximately 50 individual scans were acquired at unpredictable intervals in each subject while they were intermittently hallucinating. Immediately after each scan, subjects reported whether they had been hallucinating at that instant. Neural activity when patients were and were not experiencing hallucinations was compared in each subject and the group as a whole.

Results: Auditory hallucinations were associated with activation in the inferior frontal/insular, anterior cingulate, and temporal cortex bilaterally (with greater responses on the right), the right thalamus and inferior colliculus, and the left hippocampus and parahippocampal cortex ($P < .0001$).

Conclusions: Auditory hallucinations may be mediated by a distributed network of cortical and subcortical areas. Previous neuroimaging studies of auditory hallucinations may have identified different components of this network.

Arch Gen Psychiatry. 2000;57:1033-1038

SUBJECTS AND METHODS

SUBJECTS

Six male patients with schizophrenia and frequent auditory hallucinations were studied. Diagnosis was based on DSM-IV criteria for schizophrenia, a detailed clinical interview, and review of their hospital case notes. Patients were excluded if they had a history of head injury, neurological symptoms, speech or hearing difficulties, fulfilled DSM-IV criteria for abuse or dependence of any illicit drugs or alcohol during their lifetime, or had any contraindications to MRI scanning, including metal implants and claustrophobia. They were recruited from wards and clinics at the Maudsley Hospital, London, England. Their mean age was 35 years (SD, 11 years) with mean IQ 109 (SD, 6), measured using the National Adult Reading Test. All experienced intermittent and frequent (typically occupying half of their waking hours) auditory hallucinations of fully formed speech, mostly of a derogatory nature. Two subjects reported exclusively second-person hallucinations while the other 4 subjects described both second- and third-person hallucinations. The mean length of illness in the patients was 11 years (SD, 8 years) and all were being treated with antipsychotic medication at the time of the study: 5 with atypical antipsychotics (patient 1: clozapine, 650 mg and sodium valproate, 1.5 g daily; patient 2 and patient 3: olanzapine, 20 mg daily; patient 4: olanzapine, 30 mg daily; and patient 5: clozapine, 650 mg and sodium valproate, 1 g daily) and 1 with a conventional antipsychotic (patient 6: haloperidol injection, 50 mg monthly). All subjects provided written informed consent to enter the study, which had been approved by the Maudsley Hospital Ethics Committee.

PROCEDURE

A 1.5-T system was used to measure blood oxygenation level–dependent (BOLD) contrast, an index of neural activity, during auditory hallucinations. Two paradigms were used: (1) a novel random “sampling” method and (2) a more conventional “button-pressing” approach. The sampling method required subjects to lie at rest with their eyes closed. At randomly varied intervals of 30 to 60 seconds they heard the noise generated by the acquisition of a single volume of fMRI data (duration, 3 seconds). This served as an auditory cue for them to describe whatever they had been thinking or experiencing in the few seconds preceding the noise. They reported this verbally as soon as the noise stopped. Because there is typically a lag of 3 to 5 seconds between neural activity and the maximum BOLD signal (which reflects the local hemodynamic response to that activity), the image depicts the activity that was occurring a few seconds (usually 5 seconds) before the onset of the cue. After providing a description, subjects returned to the resting (but intermittently hallucinating) state and the procedure was repeated until a mean of 30 whole-brain 12-weighted images had been acquired from each subject. The choice of a 30- to 60-second variation between scans was a pragmatic one to keep the total acquisition time between 60 and 90 minutes per subject, the maximum that patients were able to tolerate in 1 session (the individual scan time for 2 subjects was 60 minutes, 75 minutes for 2 subjects, and 90 minutes for the other 2 subjects). Any influence of the scan noise itself is unlikely to have any effect on the BOLD response, because of the hemodynamic delay, and any nonspecific effects, such as the possibility of startle response, would be cancelled out by acquiring the baseline scans in an identical manner. Each image volume was subsequently categorized as corresponding or not corresponding to auditory hallucinations on the basis of each description. In the same session, subjects were also studied using a button-pressing method associated with activation in the left primary motor cortex, and the right cerebellum and putamen (Table).

RESULTS

All 6 subjects experienced frequent auditory hallucinations when studied with the sampling method; subjects were hallucinating during a mean of 44% of scans (range, 33%-60% of scans). Five of these patients reported auditory hallucinations during the button-pressing paradigm (hallucinating during a mean of 25% of scans; range, 5%-52% of scans), with the remaining subject reporting that the scanner noise interfered with the experience. There was no obvious periodicity in the hallucinatory activity of any individual patient.

The sampling method revealed activation associated with auditory hallucinations in the inferior frontal gyrus/insula and middle temporal gyr bilateral, particularly in the right hemisphere, where there was additional activation in the superior temporal gyrus, middle frontal gyrus, posterior parietal cortex, thalamus, and inferior colliculus. Activation was also evident in the anterior cingulate gyrus, and in the left hippocampus and parahippocampal gyrus (Table and Figure). As an index of the consistency of activation across subjects, significant right temporal activation was evident in 4 of the 6 individuals. Using the button-pressing method, there was significantly less activation of the inferior frontal and right lateral temporal gyri than with the sampling approach and there was no activation in the right middle frontal gyrus, thalamus, or inferior colliculus (even at a liberal threshold of \( P < 0.1 \)). Conversely, only the button-pressing method was associated with activation in the left primary motor cortex, and the right cerebellum and putamen (Table).

COMMENT

A striking feature of this study was the identification of an extensive network of cortical and subcortical areas associated with auditory hallucinations; previous neuroimaging studies of auditory hallucinations have typically reported less extensive activation. Thus, our earlier work using SPET linked auditory hallucinations with activation in the left inferior frontal cortex, while other studies, mainly using PET, respectively implicated the anterior cingulate gyrus, the left and the right temporal cortex, and the right temporal cortex, the left parahippocampal region and the thalamus, striatum, and cerebellum. As all of these areas were activated in the present study, these apparently inconsistent findings may have resulted from
pressing method, signaling the onset and end of discrete auditory hallucinations by pressing a button with the right index finger. The use of this more established method provided a measure of internal validity for the sampling method, as well as an index of activation related to motor response. A continuous series of 100 T2-weighted images were acquired (an image every 3 seconds) during a 5-minute period, and the timing of the button press was used to indicate which portions of this block coincided with auditory hallucinations.

**IMAGE ACQUISITION AND STATISTICAL ANALYSIS**

Gradient-echo echoplanar MR images were acquired using a 1.5-T scanner fitted with Advanced NMR hardware and software (General Electric, Milwaukee, Wis). In each of 14 noncontiguous planes parallel to the intercommissural (AC-PC) plane, 40 to 100 T2-weighted MR images depicting BOLD contrast were acquired with TE=40 milliseconds, TR=3000 milliseconds, in-plane resolution=3.1 mm, slice thickness=7 mm, slice=skip 0.7 mm. Following the minimization of movement-related artifacts by realignment and regression, voxel-wise activation maps were constructed by computing the Pearson product moment correlation of the time series at each voxel with the reported occurrence of auditory hallucinations. Ten further maps were computed at each voxel after randomly permuting the pattern of auditory hallucination reports. Following mapping of observed and randomized correlation data into standard stereotactic space, median observed and randomized maps were constructed. Foci of activation with a voxel-wise probability of type I error of <.0001 (at this level of significance one expects <1 random error voxel per slice of data) were identified by determining the critical threshold from the distribution of correlation coefficients computed following random permutation. To compare the activation with the 2 different methods of acquisition, the data from the 2 experiments were then combined and the correlation coefficients in all subjects, in both experiments, at each voxel in standard space were analyzed using the linear model below. This identified effects that were dependent on, and independent of, the experimental condition (sampling or button-pressing):

\[
\text{Corri, j} = \beta_0 + \beta_1E + \epsilon_{ij}
\]

where \(\text{Corri, j}\) is the observed correlation coefficient for subject i in group j; \(\beta_0\) is the overall mean; \(\beta_1\) is the mean correlation coefficient in experiment j; E is the classification variable coding experimental design; and \(\epsilon_{ij}\) is an error term. This model was fitted to the Talairach transformed correlation coefficients obtained by random permutation of the time series (see above) as well as the correlation coefficients obtained by the analysis of the observed time series. Fitting this model to the randomized correlation data (across the 2 groups on a voxel-wise basis) permitted the construction of distributions of \(\beta_0\) and \(\beta_1\) under the null hypothesis that there was no experimentally determined response to the sampling or button-press conditions. The null distributions of \(\beta_0\) and \(\beta_1\) were then used to determine the critical values of the 2 parameters for statistical significance at any required level of probability. We were primarily interested in differences due to the method of acquisition (sampling or button press); ie, in estimating and testing experiment-independent effects (\(\beta_0\)). However, as \(\beta_0\) is independent of \(\beta_1\), a significant value of \(\beta_0\) could arise principally due to a contribution from one of the experiments. For example, a large response in one experiment and a small one in the other may produce a mean value that is significant but that does not imply any constancy of responses in the 2 experiments. The inclusion of the \(\beta_1\) term in the model allows such responses to be identified and removed from the activation maps. Following this conservative correction of the data, significant effects were rendered onto a morphological template.

Identification of different elements of the same network. Most previous studies involved SPET or PET, which limits the number of images that can be safely acquired in each subject, and some examined a few selected regions of interest, as opposed to the entire brain.

Comparison of the 2 paradigms (one that required subjects to signal the presence of auditory hallucinations and one that did not) clarified which activations were related to the act of signaling rather than to hallucinations per se. The areas that were exclusively activated with the button-pressing method (the left precentral gyrus, the right cerebellar cortex, and the putamen) were normally engaged during voluntary movements of the right index finger. The greater activation of the right are normally engaged during voluntary movements of the middle and superior temporal gyri, thalamus, and inferior colliculus with the sampling method may reflect the internal monitoring of willed action when healthy volunteers imagine another person talking to them (auditory verbal imagery); common activation of the bilateral frontal and temporal gyri, along with right-sided precentral and inferior parietal gyri. How-
however, while imagining speech is associated with a marked activation in the supplementary motor area (SMA).\textsuperscript{24,25} This region was only weakly engaged during auditory hallucinations. Conversely, auditory hallucinations were associated with activation in the left parahippocampal re-
gion, but this region is not activated when volunteers imagine alien speech.\textsuperscript{24,25} The SMA has been implicated in the deliberate generation of inner speech,\textsuperscript{24-26} and lesions in this region are associated with the alien limb syndrome, in which the patient loses awareness that his movements are self-generated and attributes them to someone else.\textsuperscript{27} The paucity of SMA activation that we observed during auditory hallucinations might thus be related to a lack of awareness that inner speech has been generated,\textsuperscript{28} thought to be the critical deficit underlying auditory hallucinations.\textsuperscript{9} The left parahippocampal region is normally activated when subjects encounter unexpected stimuli\textsuperscript{29} and psychological models of self-
monitoring propose that it is engaged when there is a mismatch between the perceived and predicted results of cognitive activity.\textsuperscript{30} Data from previous neuroimaging studies have suggested that the left parahippocampal gyrus, ventral striatum, and prefrontal cortex could form a network of regions responsible for self-monitoring.\textsuperscript{10} Parahippocampal activation during auditory hallucinations may thus represent a neural (but not necessarily conscious) response to internal speech that subjects are unaware they have generated.

The prominent involvement of the right hemisphere during auditory hallucinations may seem surprising given that the patients were perceiving speech, but is consistent with data from previous neuroimaging\textsuperscript{2-3} and electroencephalographic studies\textsuperscript{31} of auditory hallucinations, and with the greater right fronto-temporal activation when subjects imagine another person’s speech as opposed to their own.\textsuperscript{25} Moreover, as auditory hallucinations in schizophrenia are typically derogatory and hostile in tone, the prominent engagement of right hemispheric areas might reflect processing of the prosody\textsuperscript{32} and inference of what is being said,\textsuperscript{33} as well as an emotional response to its content.\textsuperscript{34} A methodological limitation of this study, common to all investigations using the cognitive subtraction method, is the lack of knowledge about the resting brain activity in patients and whether it is different from resting activity in other nonhallucinating schizophrenic patients and in normal individuals. We are planning to investigate this using the sampling technique in future studies. A further limitation of the sampling approach is that it is less precise about the actual timing of the hallucinations, such as the length of the preceding hallucinatory experience, and is reliant on the accuracy of self-report. It is difficult to find large numbers of patients suitable for this type of study and the relatively small sample size could serve to reduce the validity of the findings. However, we attempted to overcome the limitations of small numbers by using fMRI to acquire a larger number of images and using both the sampling and button-pressing technique within the same scanning session, accepting differences in noise and acquisition method, to allow comparison with each other (as an internal control) and the previous button-pressing literature.

In conclusion, this study suggests that auditory hallucinations involve a distributed network of cortical and subcortical areas. This is consistent with the notion that
auditory hallucinations arise through the disruption of normal cognitive processes, such as monitoring of self-generated verbal material, rather than a result of an epileptiform focus in auditory cortex. The engagement of both cortical and subcortical elements of the auditory pathway during hallucinations makes it easier to appreciate why patients often describe these experiences as indistinguishable from “real” auditory perceptions. Defining the brain areas that mediate auditory hallucinations facilitates our understanding of their basis in cognitive, as well as biological, terms and provides a scientific rationale for their treatment using recently developed psychological and biological strategies that are currently undergoing clinical evaluation.

Accepted for publication May 23, 2000.

Dr Shergill is supported by a Wellcome clinical training fellowship.

We thank Chris Andrew, Edson Amaro, MD, Sophia Frangou, MD, Andrew Simmons, PhD, and the neuroimaging staff for technical support.

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