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Subcortical Modulation in Auditory Processing and Auditory Hallucinations

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Abstract

Hearing perception in individuals with auditory hallucinations has not been well studied. Auditory hallucinations have previously been shown to involve primary auditory cortex activation. This activation suggests that auditory hallucinations activate the terminal of the auditory pathway as if auditory signals are submitted from the cochlea, and that a hallucinatory event is therefore perceived as hearing. The primary auditory cortex is stimulated by some unknown source that is outside of the auditory pathway. The current study aimed to assess the outcomes of stimulating the primary auditory cortex through the auditory pathway in individuals who have experienced auditory hallucinations. Sixteen patients with schizophrenia underwent functional magnetic resonance imaging (fMRI) sessions, as well as hallucination assessments. During the fMRI session, auditory stimuli were presented in one-second intervals at times when scanner noise was absent. Participants listened to auditory stimuli of sine waves (SW) (4 kHz-5.5 kHz), English words (EW), and acoustically reversed English words (arEW) in a block design fashion. The arEW were employed to deliver the sound of a human voice with minimal linguistic components. Patients' auditory hallucination severity was assessed by the auditory hallucination item of the Brief Psychiatric Rating Scale (BPRS). During perception of arEW when compared with perception of SW, bilateral activation of the globus pallidus correlated with severity of auditory hallucinations. EW when compared with arEW did not correlate with auditory hallucination

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severity. Our findings suggest that the sensitivity of the globus pallidus to the human voice is associated with the severity of auditory hallucination.

Introduction

Although auditory hallucinations are one of the most common symptoms in schizophrenia, the underlying mechanism is not clearly understood [1]. Neural activity during auditory hallucinations has been studied and results indicate the involvement of language-related regions. Activation of the superior temporal cortex (primary auditory cortex) has been previously shown while auditory hallucinations were occurring [2,3]. In addition, Broca's and Wernicke's areas and their right hemisphere homologues, have also been shown to be activated during auditory hallucinations [4]. The activations in these areas are consistent with the phenomenology of auditory verbal hallucinations, in which someone experiences hearing words or sentences [5]. Thus, the primary auditory region of the superior temporal cortex activation manifests as the experience of hearing with Broca's area activation reflecting phonological and grammatical processing of words and/or sentences, and Wernicke's area activation reflecting the semantic/meaning processing of what is heard.

Although external auditory input would be expected to activate the same regions as those activated during auditory hallucinations, it is not well understood whether processing of non-hallucinatory external sound is impacted by the presence of auditory hallucinations. Specifically, the activation of primary auditory cortex during the experience of auditory hallucination corresponds to the fact that auditory hallucinations are perceived as an experience of actual hearing. Despite the absence of the physical acoustic input, the primary auditory region in the superior temporal lobe is activated, which accounts for the generation of hearing sensation. It is implicated that auditory processing and language processing may be affected in patients with auditory hallucination. However, the extent to which activation of the auditory and language cortices, in response to language and non-language stimuli, may differ in individuals who experience auditory hallucinations is not clear.

Auditory hallucinations have been found to be associated with differential neural activity in response to actual external auditory input. In an oddball tone fMRI study, subjects with auditory hallucinations showed greater activity in the left primary auditory cortex as compared to a patient control group without auditory hallucinations [6]. Moreover, schizophrenia patients with hallucinations evidence a laterally shifted mismatch negativity peak relative to a non-hallucinating group who showed more posterior mismatch negativity compared to a non-clinical group [7]. These differential neural responses may suggest increased sensitivity to external auditory input in individuals with auditory hallucinations. However, to date, there have been no studies examining neural response to external human voices in subjects with auditory hallucinations.

Therefore, in order to determine and isolate the neural responses to external human voices in patients with auditory hallucinations, we tested the association between neural responses to external human voice input and the self-reported severity of auditory hallucinations.

Methods

Sixteen (9M/7F) patients with schizophrenia were recruited from the Zucker Hillside Hospital in Glen Oaks, NY. Diagnoses were based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) [8] and supplemented with medical records and information from clinicians when available. All patients were native English speakers and met DSM-IV criteria for schizophrenia or schizoaffective disorder and were being treated with atypical antipsychotic medications. The mean age of patients was 42.0 (SD = 8.85) years. Exclusion criteria included left-handedness, MR imaging contraindications, serious medical conditions and hospitalization in the prior six months. This study was approved by the North Shore Long Island Jewish Medical Center Institutional Review Board and written informed consent was obtained from all study participants.

Participants were assessed with the 18-item Brief Psychiatric Rating Scale (BPRS)[9] before the MR imaging exam, including a hallucinatory behavior item. The BPRS hallucination item was modified to specifically ask about auditory hallucinations experienced in the past week. In statistical analysis, this auditory hallucination question, rated from (1-7) was used in estimating the severity of auditory hallucinations.

A total of 456 echo-planner imaging (EPI) volumes were acquired in three runs on a GE 3T HDx MR imaging system (TR=3000 ms, TE=27 ms, matrix = 64*64, FOV = 240 mm, slice thickness = 3 mm, 40 contiguous oblique axial slices), 152 volumes * 3 runs using fast Sparse Temporal Sampling [10]. Auditory stimuli (400 ms) were binaurally presented via air-conducted headphones within a non-EPI period (1000 ms) followed by EPI acquisition (2000 ms).

During each run, there were three conditions; sine waves (SW) (4 kHz-5.5 kHz), English words (EW), and acoustically reversed English words (arEW), each of which had four blocks. The order of blocks were pseudo-randomized across three fMRI runs so that the block order would be counterbalanced. Words in the EW condition were one syllable and had a Kucera-Francis written frequency of 9 or higher [11]. The stimuli in the arEW condition were created by reversing the stimuli in the EW condition. Therefore, EW and arEW conditions had identical acoustic properties, except for the reversal. Words in the EW condition had three segments (plosive consonant, vowel and plosive consonant), so that plosive consonants at the onset and coda would prevent coincidental recognitions in the reversed counterpart condition (arEW). The frequency range of 4-5.5kHz in the SW condition was chosen to avoid the fundamental frequency range in the EW and arEW conditions.

Each block was 24 seconds long followed by 12 seconds of a resting period. In a block, 8 epochs of auditory stimuli were presented. Participants were asked to press the button when they heard the identical sound twice in a row (i.e., one-back task), in order to retain their attention to the sound presented. The arEW were employed to deliver the sound of a human voice with minimal linguistic components.

Imaging data were analyzed using FMRI Expert Analysis Tool (http://www.fmrib.ox.ac.uk/analysis/research/feat) in the FMRIB Software Library (FSL: http://www.fmrib.ox.ac.uk/

fsl/). Images were motion corrected, linearly registered to the SPGR structural volume (TR = 7.5 ms, TE = 3 ms, Inversion Time = 650ms, flip angle = 8°, matrix = 256×256, FOV = 240 mm, 216 contiguous 1 mm thick coronal images), normalized to the standard MNI template via the co-registered structural volume and smoothed using an 8 mm FWHM Gaussian Kernel.

Voxelwise one-way t-tests were conducted for arEW-SW, EW-arEW, and EW-SW contrasts, to assess the regions that are specifically activated during greater frequency distribution and human-voice property (Acoustic: arEW-SW), phonological and lexical processing (Linguistic: EW-arEW), and acoustic and linguistic processing altogether (EW-SW). The arEW-SW acoustic contrast was intended to isolate human voice and associated frequency distribution. While the SW condition delivers a sound of a specific frequency, the arEW condition introduces human voices that have a broader frequency range. The EW-arEW linguistic contrast was used to elucidate phonological and semantic processing. The EW condition, but not the arEW condition, would induce phonological and semantic processing, while these two conditions are acoustically equivalent and have human voice properties. The EW-SW contrast would reflect the sum of arEW-SW and EW-arEW. For each contrast, voxelwise regression tests were performed to test the association between the hallucination severity and these contrasts. For each of these four voxelwise tests, Z statistic images were estimated where clusters were determined by voxel $Z > 1.65$ with a familywise error-corrected cluster significance threshold of p=005 assuming a Gaussian random field for the Z-statistics.

Results

Among 16 participants, eight of them reported no hallucinatory experience (BPRS rating = 1) in the past week. The other eight had minimum to severe hallucinatory experience (2 to 7). The mean rating for the auditory hallucination questionnaire was 2.31 (SD=1.49). Nine participants were on atypical antipsychotics (Aripiprazole 15-30mg/day, Clozapine 200-450mg/day, Risperidone 3-4mg/day, Quetiapine 300mg/day), four participants were on typical antipsychotics (Haloperidole Decanoate 30-33.33mg/week equivalent, Fluphenazine 45mg/week) and three were on both (Aripiprazole 15mg/day or Quetiapine15mg/day and Fluphenazine 3-10mg/day or Haloperidole 5mg/day). No patient reported experiences of auditory hallucination on the day of the exam.

The arEW-SW contrast revealed activation in the superior temporal cortices bilaterally, having peak coordinates at [MNI: −62, −16, 2 (p=0.0005) and 56, −18, −14 (p=0.0075)] (Figure 1). The arEW-SW contrast also showed association with the BPRS hallucination score. One cluster (1608 voxels, peak at [MNI: −24, −42, 6 (p=0.036)]) showed significant positive association between hallucination severity and the arEW-SW contrast in the posterior basal ganglia (Figure 2). This cluster was mostly located within the bilateral global pallidus. There was no cluster that showed a significant negative association between hallucination severity and this contrast.

The EW-arEW contrast showed activation centered in the left inferior frontal gyrus (21823 voxels, peak [MNI: −46, 28, 16 (p<0.00001)]). However, no cluster was found in association with hallucination severity.

The EW-SW contrast revealed activations that are nearly the sum of arEW-SW and EW-arEW contrasts. Two clusters covered the left and right superior temporal gyrus (Left: 8605 voxels, peak [MNI: −66, −30, −4] and Right: 4515 voxels, peak [MNI: 66, −14, −4]), in which the left inferior frontal gyrus was included within the left cluster. No cluster was found to be associated with hallucination severity.

Hit rate for the one-back task was 88.8% (SD=4.55%), which did not show significant correlation with the BPRS auditory hallucination question or globus pallidus activation or superior temporal cortex activation. No other BPRS scores showed significant correlation with globus pallidus activation and superior temporal cortex activation.

Discussion

To our knowledge, this is the first fMRI study in which human voices were presented during MRI scanning to assess whether auditory processing differs in individuals who have recently experienced auditory hallucinations. The globus pallidus activation showed an association with the level of reported auditory hallucinations when human voices were presented.

Both the arEW-SW and EW-arEW fMRI contrasts activated the anticipated regions. Specifically, the arEW-SW acoustic contrast showed activations in the superior frontal lobe, which corresponds to the task design where broader auditory frequency range would stimulate greater area in the superior temporal lobe. The EW-arEW linguistic contrast showed activation in the language cortices including Broca's area, which follows from the fact that the EW but not the arEW condition has linguistic components. While the activated regions in these two contrasts did not show associations with hallucination severity, the results favor the validity of the design to isolate activations for broader frequency in the arEW-SW contrast and linguistic stimulation in the EW-arEW contrast. Activations in these two contrasts independent of the hallucination status support that auditory inputs in the current study delivered intended stimuli to evoke acoustic and linguistic neural activities.

There are a few alternative explanations for the observation of greater activation in the globus pallidus in individuals with more severe auditory hallucinations. It has been previously hypothesized that subvocal activities are increased during auditory hallucinations [12], and the globus pallidus has been shown to be activated during speech articulation [13]. Thus, it is feasible to speculate that the globus pallidus is involved in the subvocal activities occurring during auditory hallucination. However, the greater activation in the globus pallidus found in the current study is in the arEW-SW contrast, the comparison of the human voice to sine waves. The activation of the globus pallidus in the absence of articulation but during auditory perception could be accounted for by the motor theory of speech perception [14,15]. There has been mounting evidence in favor of the motor theory of speech perception, in which speech perception has been shown to be affected by speech production process/rehearsal [16–18]. In the arEW-SW contrast, the globus pallidus showed the positive

association with auditory hallucination, implicating the sensitivity to human voice as a function of auditory hallucination. There was no association found between EW-SW contrast and hallucination severity. We interpret that the effect of human voice found in arEW-SW was washed out because of the ample linguistic content included in the EW condition.

Alternatively, it is also possible to interpret that the globus pallidus is mediating attentional control rather than voice-specific processing. The basal ganglia have been implicated in treatment intervention of schizophrenia [19], as well as its dopaminergic relation to the schizophrenia pathology [20]. Specifically, disrupted attention has been proposed to be involved in hallucinations [21,22] and attention has been shown to modulate auditory hallucination in non-clinical individuals with auditory hallucination [23,24]. While the effectiveness of atypical antipsychotics to hallucinations are well known [25], atypical antipsychotics were shown to reduce the globus pallidus activation during an attentional control task resulting in improved attentional control [26]. Thus, the current finding, where the globus pallidus activation correlated with hallucination severity, could be interpreted as a sign of disrupted attention in individuals with greater hallucination severity, specifically to the external auditory human voice, which usually is a form of actual auditory hallucinations. We would argue, however, that the current results favor the subvocal interpretation rather than the attentional interpretation, because non-hallucinatory BPRS, including thought disturbances, did not show a significant correlation with the globus pallidus activation. In addition, the 1-back performance, which would reflect their attention, did not show association with pallidal activations.

There are a few limitations of the current study that have to be addressed. First, the arEW vs. SW contrast is not exclusively human voice vs. other sound. In addition to the human voice features, arEW stimuli had a greater frequency distribution than SW stimuli, which were pure sine waves that varied within a limited frequency range across events (4 kHz-5.5 kHz). Therefore, the arEW - SW contrast might instead be a function of the difference in the frequency range. Furthermore, human voice in arEW may deliver different salience compared to SW, which prevent us to give clearer interpretation for the globus pallidus activation. In an ideal comparison between human voice vs. other sounds, sounds with similar frequency distribution should be presented.

While our sample size was sufficient to detect significant corrected effects, further investigations in larger samples may help isolate other associations between auditory hallucination severity and functional activation. We failed to detect any association in the EW – arEW contrast. The lack of a statistically significant difference between these two conditions may be due to the absence of language processing deficits in individuals with auditory hallucinations.

In the current study, participants were asked about their experience of auditory hallucination in the previous week. This would capture hallucinatory state in the previous week, which would reflect the underlying trait or temporary state of having auditory hallucination. It remains an open question whether emergence of auditory hallucination in schizophrenia is due to their underlying trait or is a state that is experienced under certain conditions.

In summary, the current study indicates that auditory hallucinations are associated with globus pallidus activation in response to human voice perception. In future studies, greater variety of auditory stimuli would enable the detection of the exact process sensitized in auditory hallucinations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- fMRI study, using external auditory stimuli, in patients with auditory hallucinations
- Severity of auditory hallucinations was associated with activation in response to human voice stimuli
- The association was found in the Globus Pallidus

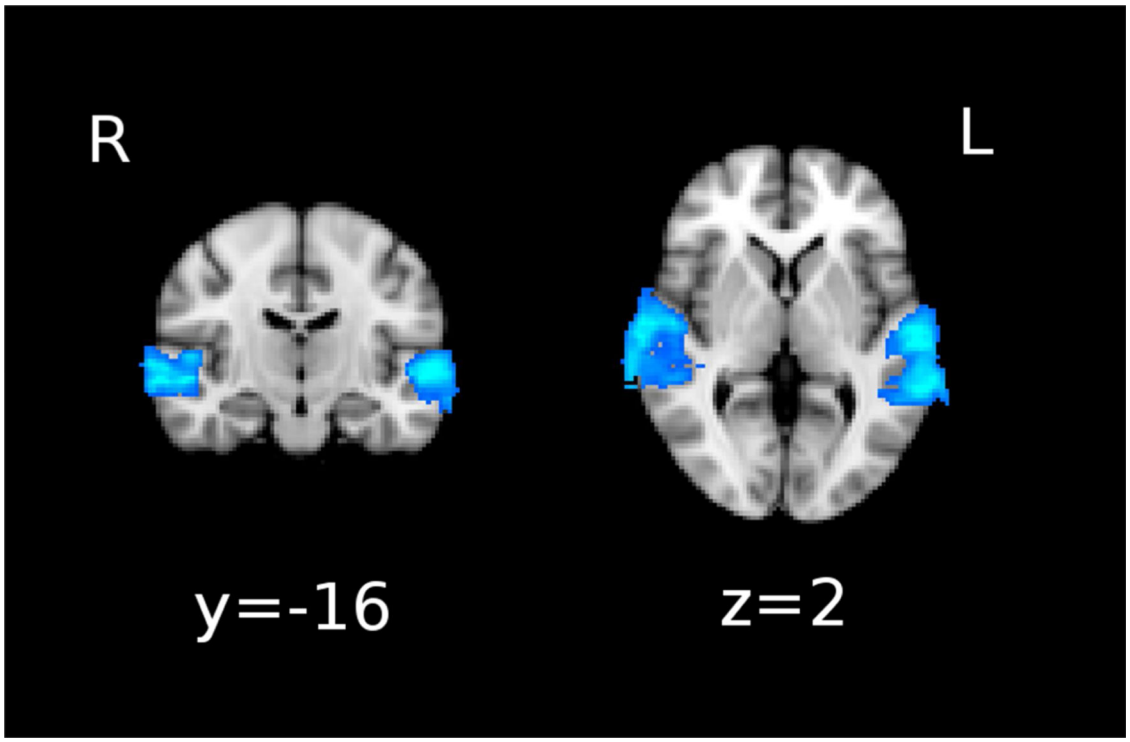

Figure 1.
Activation in arEW-SW contrast. Z>1.65, corrected.

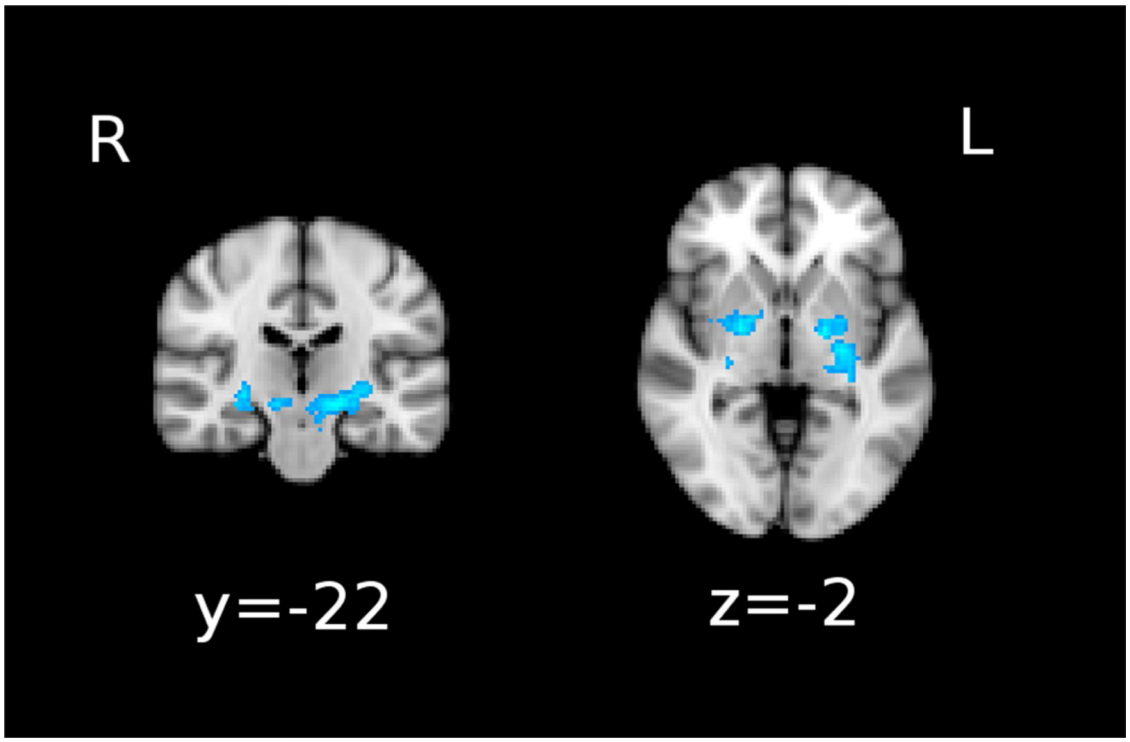

Figure 2.
Regions that showed association between BPRS auditory hallucination scale and arEW-SW contrast. Z>1.65, corrected.