Behavioural Brain Research 295 (2015) 78–81

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Subcortical modulation in auditory processing and auditory hallucinations☆

Toshikazu Ikuta[a,*], Pamela DeRosse[b,c], Miklos Argyelan[b,c], Katherine H. Karlsgodt[b,c,d], Peter B. Kingsley[e], Philip R. Szeszko[b,c,d], Anil K. Malhotra[b,c,d]

[a] Department of Communication Sciences and Disorders, School of Applied Sciences, University of Mississippi, University, MS 38677, USA
[b] Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research, Manhasset, NY, 11030, USA
[c] Division of Psychiatry Research, Zucker Hillside Hospital, North Shore—LIJ Health System, Glen Oaks, NY, 11004, USA
[d] Hofstra North Shore—LIJ School of Medicine, Departments of Psychiatry and Molecular Medicine, Hempstead, NY, USA
[e] Department of Radiology, North Shore University Hospital, Manhasset, NY, 11030, USA

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.

ARTICLE INFO

Article history:
Received 22 October 2014
Received in revised form 6 August 2015
Accepted 9 August 2015
Available online 11 August 2015

Keywords:
Auditory hallucinations
fMRI
Schizophrenia
Hearing
Auditory processing

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) (4–5.5 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 severity. Our findings suggest that the sensitivity of the globus pallidus to the human voice is associated with the severity of auditory hallucination.

1. 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

☆ This work was supported in part by grants from NARSAD Young Investigator Award (TI), NSLIJ Research Institute General Clinical Research Center (M01 RR018535), an Advanced Center for Intervention and Services Research (P30 MH090590) and a Center for Intervention Development and Applied Research (P50 MH080173).
* Corresponding author at: Department of Communication Sciences and Disorders, School of Applied Sciences, University of Mississippi, 311 George Hall, 352 Rebel Drive, PO Box 1848 University, MS 38672-1848, USA.
E-mail address: tikuta@olemiss.edu (T. Ikuta).

http://dx.doi.org/10.1016/j.bbr.2015.08.009
0166-4328/

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.

2. 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 to 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) (4–5.5 kHz), English words (EW), and acoustically reversed English words (arEW), each of which had four blocks. The order of blocks was 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 4–5.5 kHz in the SW condition was chosen to avoid the fundamental frequency range in the EW and arEW conditions.

Each block was 24 s long followed by 12 s 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 = 650 ms, 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 dis-

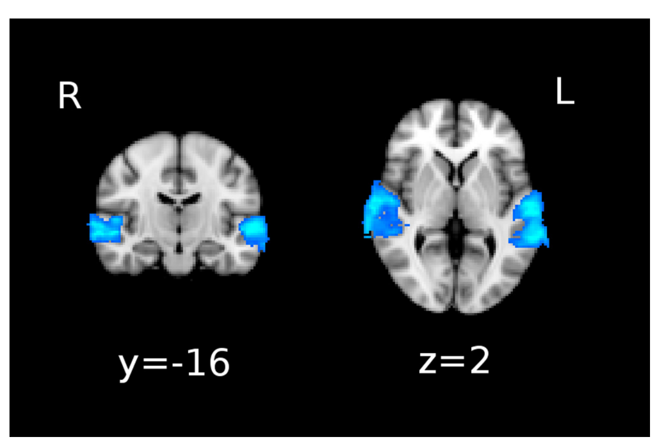

Fig. 1. Activation in arEW–SW contrast. $Z > 1.65$, corrected.