Neural Signature for Auditory Hallucinations in Schizophrenia: A High-Resolution Positron Emission Tomography Study with Fludeoxyglucose (18F)

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Objective: Auditory hallucinations (AHs) are a core symptom of schizophrenia. We investigated the neural signature of AHs by comparing hallucinating patients with schizophrenia with non-hallucinating patients with schizophrenia.

Methods: We recruited hallucinating patients with schizophrenia meeting the criteria for persistent, prominent, and predominant AHs (n=10) and non-hallucinating patients with schizophrenia (n=12). Various clinical assessments were performed including Psychotic Symptom Rating Scale for Auditory Hallucinations. Using fludeoxyglucose (18F) positron emission tomography, regional differences in neural activity between the groups were analyzed.

Results: The regions of interest analysis showed significantly lower standardized uptake value ratio (SUVR) in the superior, middle, and inferior frontal gyri, and higher SUVR in the putamen in patients with AHs versus patients without AHs. These findings were confirmed in the voxel-wise analysis.

Conclusion: Our findings indicate that hypoactivity in the frontal and cingulate gyri, coupled with hyperactivity in the temporal gyrus and putamen, may contribute to the pathophysiology of AHs.

KEY WORDS: Auditory hallucinations; Schizophrenia; Positron-emission tomography; Bottom-up; Top-down.

INTRODUCTION

Auditory hallucinations (AHs) occur in the general population at a median estimated rate of 4% to 5%.1 In patients with schizophrenia, the prevalence is quite common, up to 74%.2 Moreover, 25% to 50% of subjects continue to experience them despite medication.3,4 The experience of voices can impact on quality of life, self-esteem, anxiety, depression, suicide attempts, and cognitive function.5-7 Determining the pathophysiological basis of AHs is important for understanding the neurobiological processes underlying schizophrenia and for the development of more effective treatment strategies for patients who are unresponsive to existing therapies. Despite extensive research, little is known about the neurobiology underlying this phenomenon.

Over recent decades, neuroimaging research has attempted to determine the neural mechanism(s) involved in the development of AHs in patients with schizophrenia. Volumetric studies have consistently reported that severity of AHs is associated with reduced relative volume in the left auditory cortex, left amygdala, left insula, and prefrontal cortex.8-10 In parallel, functional neuroimaging studies have uncovered various areas associated with AHs. In a meta-analysis, it was reported that hallucinators
showed increased activation likelihoods in a distributed bilateral frontotemporal network that included Broca’s area, the anterior insula, the precentral gyrus, the frontal operculum, middle and superior temporal gyri, the inferior parietal lobule, the hippocampus, and the parahippocampal region. Results from the meta-analysis supported two hypotheses: (1) aberrant activation within frontotemporal language areas during AH and (2) dysfunction in the verbal memory system that could lead to the occurrence of AH.

To capture the neurobiological underpinnings of AHs directly, it is important to recruit patients with prominent and persistent AHs and to distinguish on- and off-set of AHs within an imaging session. Several functional magnetic resonance imaging (fMRI) studies used a button-pressing approach and a random-sampling method to capture brain processes directly involved in generating AHs. However, the scanner noise generated during fMRI procedures can activate the auditory cortex and mask neural activity due to AHs. Positron emission tomography (PET) imaging is a relatively quiet process despite its lower spatial and temporal resolution versus fMRI. Only two reported PET studies selected homogeneous patients with prominent and frequent AHs and checked for the occurrence of AHs during the scanning process. They reported higher metabolic rates in the left superior and middle temporal cortices, bilateral superior medial frontal cortex, and left caudate nucleus in patients with AHs versus non-hallucinating patients. Problems with those studies included that the time duration of AHs during the scanning process was not provided.

Comparing the neural activities in schizophrenic patients with AHs with those in normal controls would produce findings related not only to the neural correlates of AHs but also to disease-related neural correlates. Therefore, we thought that comparison between patients with AHs and without AHs would uncover distinctive neural correlates of AHs by avoiding the confounding effects of disease-related symptomatology other than AHs. This study was undertaken to investigate regional differences in neural activity between patients with and without AHs and to explore relationships between glucose metabolism and severity of AHs using high-resolution fluodeoxyglucose (18F) ([18F]FDG)-PET.

**METHODS**

**Participants**

We recruited 10 patients with schizophrenia reporting persistent, prominent, and predominant AHs and 12 age- and gender-matched patients with schizophrenia reporting no AHs at least for the past 3 months or no experience of AHs ever. Patients were screened at Chonbuk National University Hospital in Jeonju, Korea. Diagnoses were established using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). The characteristics of AHs were defined as follows: persistent as sustained over the past 3 months, prominent as occurring ≥10 times/day and 3 days/week, and predominant as Positive and Negative Syndrome Scale (PANSS) P1 score ≤3 (mild) and P3 score ≥4 (moderate). Exclusion criteria were alcohol or drug abuse within the last 6 months, claustrophobia, history of head trauma, other neurological disorders, pregnancy, and significant medical problems.

This study was approved by the ethical committees of Chonbuk National University Hospital (approval number: 2012-07-014) and Gachon University Gil Medical Center (approval number: GIRBD0027-2012) where the PET and MRI scans were performed. All participants gave oral and written informed consent after the objectives and procedures of the study had been explained.

**Assessment**

Within 1 week before PET imaging, psychopathology was evaluated by experienced psychiatrists using the PANSS, Calgary Depression Scale for Schizophrenia (CDSS), and Social and Occupational Functioning Assessment Scale. The Prospective and Retrospective Memory Questionnaire (PRMQ) was also used to measure the level of cognitive functioning. The scores of the prospective and retrospective subscales of the PRMQ were calculated by summing the scores of items 1, 3, 5, 7, 10, 12, 14, and 16, and the rest of the items, respectively. On the day of PET imaging, the Psychotic Symptom Rating Scale for Auditory Hallucinations (PSYRATS-AH) was used before the [18F]FDG injection. All participants were right-handed. The 11 items of the PSYRATS-AH assess different dimensions of AHs and can be clustered in three factors: a physical characteristics factor (frequency, duration, location, and loudness), an emotional characteristics factor (amount and degree of negative content...
Acquisition and Reconstruction of PET and MRI Data

All patients were scanned with a high-resolution research tomograph (HRRT)-PET (Siemens, Knoxville, TN, USA) and a 7-T MRI (Magnetom; Siemens, Erlangen, Germany). The HRRT-PET is an ultra-high-resolution brain-dedicated PET scanner that has a transaxial in-plane resolution of 2.5-mm full width at half maximum (FWHM).24,25) All patients fasted for at least 6 hours before $[^{18}F]$FDG PET scanning. A bolus injection of $[^{18}F]$FDG (injected dose, 192.5±12.6 MBq) was administered intravenously. During uptake of $[^{18}F]$FDG into the brain, patients were seated on a bed for 30 minutes. During $[^{18}F]$FDG uptake, all patients measured the duration of AHs themselves using a stopwatch. After $[^{18}F]$FDG uptake, an emission scan was performed in static scan mode for 30 minutes. After the emission scan, a transmission scan was conducted for 6 minutes 10 seconds using a $^{137}$Cs point source for attenuation correction. After $[^{18}F]$FDG PET scans, 7-T MRI was scanned using a three-dimensional T1-weighted magnetization-prepared rapid gradient echo (3D T1MPRAGE) sequence for structural brain imaging. 3D T1MPRAGE images were acquired with the following parameters: repetition time (TR)=1,900 ms, echo time (TE)=3.73 ms, inversion time (TI)=1,100 ms, flip angle=10°, voxel size=0.75×0.75×0.75 mm³, and number of slices=256.

PET images were reconstructed using the 3D-ordinary Poisson ordered-subset expectation maximization (OP-OSEM3D) algorithm that was accelerated using symmetry and single-instruction multiple-data-based projection and back-projection techniques.26) The reconstructed PET images were post-processed with decay correction and had a matrix of 256×256×207 and iso-voxel resolution of 1.22×1.22×1.22 mm³. For the calculation of the $[^{18}F]$FDG standardized uptake value ratio (SUVR), the $[^{18}F]$FDG PET emission data were reconstructed as a single frame.

Data Processing and Statistical Analysis

None of the patients with AHs was excluded because they all experienced AHs during the 30 minutes of $[^{18}F]$FDG uptake. Images were inspected visually for motion artifacts by an expert in PET image quality assurance. Spatial preprocessing and statistical analyses of the PET images were performed in Statistical Parametric Mapping 8 (SPM8; Wellcome Trust Centre for Neuroimaging, UK; http://www.fil.ion.ucl.ac.uk/spm). For spatial preprocessing, each patient’s PET image was coregistered to the same patient’s MRI image. Then, all MRI images with coregistered PET images were spatially normalized into the Montreal Neurological Institute (MNI) template used in SPM8. Finally, spatially normalized PET images were smoothed with a Gaussian kernel of 6-mm FWHM. To calculate $[^{18}F]$FDG SUVR values, the intensity value of each voxel in the PET image was divided by the mean intensity of all intracerebral voxels.27) The $[^{18}F]$FDG SUVR values were obtained in 116 predefined regions of interest (ROIs) using the automated anatomical labeling (AAL) program.28)

Demographic and clinical data were compared between the groups using two-tailed $t$ test or chi-square test. To compare regional glucose metabolism between the groups, we performed ROI-based analyses and voxel-based analyses. For the ROI-based analyses, 90 ROIs, excluding the cerebellum and vermis, were selected based on a literature review.29) A two-tailed $p$ value $<0.05$ was considered to indicate a statistically significant value. In the voxel-based analysis, the level of statistical significance was set as $p<0.005$, uncorrected, with a minimum cluster size of 20 adjacent voxels. Between-group comparisons on regional $[^{18}F]$FDG SUVR values were performed using a two-tailed $t$ test or analysis of covariance (ANCOVA), as appropriate. The correlations between the $[^{18}F]$FDG SUVR values and the severity of AHs assessed using PSYRATS-AH in patients with AHs were not analyzed because of small sample size. In ROI-based analysis, a two-tailed probability value of $p<0.05$ was chosen as a statistically significant value. In voxel-based analysis, the level of statistical significance was defined as $p<0.005$ uncorrected with a minimum cluster size of 20 adjacent voxels. To correct for multiple comparisons, results were further analyzed using thresholds of family wise error (FWE) and false discovery rate (FDR) at $p<0.05$.

RESULTS

Demographic and clinical data of patients with AHs (AH group) and without AHs (non-AH group) are sum-
Table 1. Demographic and clinical characteristics of the participants

| Variable                              | Schizophrenia | p value |
|---------------------------------------|---------------|---------|
|                                       | With AHs (n=10) | Without AHs (n=12) |       |
| Age (yr)                              | 39.20±10.55   | 31.00±9.09   | <0.064 |
| Education (yr)                        | 14.00±1.89    | 13.83±1.99   | <0.843 |
| Married state, single/married/divorced| 8/1/1         | 8/2/2        | 1.000  |
| Sex, male/female                      | 7/3           | 8/4         | 1.000  |
| Age of onset (yr)                     | 26.80±9.44    | 20.08±7.81   | <0.082 |
| CDSS                                  | 8.00±5.44     | 3.50±4.08    | <0.038*|
| Chlorpromazine equivalence (mg/day)   | 856.00±654.17 | 340.42±285.49| <0.023*|
| Duration of illness (mo)              | 136.20±76.07  | 112.50±78.01 | <0.481 |
| PANSS total                           | 51.10±9.86    | 40.92±9.09   | <0.020*|
| PRMQ Prospective                      | 17.30±4.90    | 14.83±6.39   | <0.330 |
| PRMQ Retrospective                    | 18.30±6.3     | 13.00±4.86   | <0.039*|
| PSYRATS-AH Total                      | 24.50±6.47    | 2.08±7.22    | <0.001*|
| Physical characteristics              | 9.10±1.45     | 0.67±2.31    | <0.001*|
| Emotional characteristics             | 8.80±4.76     | 0.92±3.18    | <0.001*|
| Cognitive interpretation              | 6.60±1.90     | 0.50±1.73    | <0.001*|
| SOFAS                                 | 59.00±10.75   | 66.67±11.93  | <0.132 |

Values are presented as mean±standard deviation or number only.

AHs, auditory hallucinations; CDSS, Calgary Depression Scale for Schizophrenia; PANSS, Positive and Negative Syndrome Scale; PRMQ, Prospective and Retrospective Memory Questionnaire; PSYRATS-AH, Psychotic Symptom Rating Scales-Auditory Hallucinations; SOFAS, Social and Occupational Functioning Assessment Scale.

*Statistically significant.

Significant differences between the groups were observed in the CDSS, chlorpromazine equivalence, PANSS total and −positive subscale total, PSYRATS-AH, and PRMQ retrospective subscale. For the PANSS subscales, only the positive scale score was significantly different between the groups (p=0.002). The durations (second) of AHs that occurred in the [18F]FDG uptake were 787.64±684.48 (range, 48.55-1,742.21) and 0 for the AH and non-AH groups, respectively.

As for the results on group differences, the ROI analysis demonstrated significantly lower SUVR in the orbital parts of right middle and inferior frontal gyri and medial parts of the superior frontal gyrus and higher SUVR in the left and right putamen in patients with AHs versus patients without AHs (Table 2). However, when controlled for the confounding factors (the CDSS, PRMQ retrospective subscale, and chlorpromazine-equivalent doses), no finding remained significant. The voxel-based analysis revealed greater activation in the left middle and inferior temporal gyri, left putamen, left and right fusiform gyri, and left cerebellum (p<0.005, uncorrected) and less activation in the left superior, middle, and inferior frontal gyri, right inferior frontal gyrus, left precentral gyrus, and left and right middle cingulate gyri (p<0.005, uncorrected) in the AH group versus the non-AH group (Table 3, Fig. 1). When corrected for the confounding factors including age and multiple comparisons, these findings were no longer significant.
DISCUSSION

To determine the neural basis of AHs, we compared SUVR between patients with and without AHs and investigated correlations between SUVR and severity of AHs using [18F]FDG-PET. To enhance the homogeneity of the AHs, characteristics for persistent, prominent, and predominant AHs were clearly predefined. In the AH group, we observed hyperactivity in the putamen and temporal gyrus, and hypoactivity in several parts of the frontal gyrus and cingulate gyrus compared with the non-AH group. These findings support a neurocognitive model in which both bottom-up and top-down processes interact to produce these erroneous percepts.29,30

With regard to the results of frontal activity, implicated in the pathogenesis of AHs, several studies have reported hyperactivity in the right medial prefrontal gyrus,31 medial and superior frontal gyri,12 and the frontal operculum.11 However, hypoactivity has also been reported in the left premotor cortex33 and bilateral superior frontal gyrus.34 In the present study, we observed hypoactivity in the superior, middle, and inferior frontal gyri in both ROI and voxel-based analyses (albeit at an uncorrected level). Hypoactivity has been demonstrated in trait studies33,34 comparing patients experiencing AHs with patients without AHs or healthy controls during tasks with verbal material or auditory stimuli. That is, they investigated the neural bases of the susceptibility to hallucinate, independent of the subjects’ experience during scanning. As our study did not use a task during [18F]FDG uptake and all subjects in the AH group experienced AHs during uptake, our results may re-
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Fig. 1. Statistical parametric maps showing group differences: greater activation in the temporal gyrus and the putamen and lesser activation in the frontal and cingulate gyri in the auditory hallucinations (AHs) group compared to the non-AHs group (cluster size=20, \( p < 0.005 \), uncorrected). MNI, the Montreal Neurological Institute template.

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flect direct measures of brain activation associated with AHs. In this regard, this is the first reported study demonstrating hypoactivity in the frontal areas as a neural mechanism of AHs. However, it should be noted that our findings may be associated with depression in patients with AHs, not with AHs per se, because the score of the CDSS was significantly higher in patients with AHs compared to patients without AHs and positive findings were disappeared when controlling for depression. A recent meta-analysis on the changes of brain activity in depression reported that in resting condition, increased correlated activity was observed in the left amygdala, left parahippocampus, left claustrum, left putamen, right thalamus, and right posterior cerebellum and decreased activity was shown in the left superior temporal, right anterior cingulate, and left middle frontal regions under resting conditions.\(^{35}\) In future study, it would be critical to recruit participants without depression or groups without difference in depression severity. Nonetheless, implications of the findings may be as follows. The superior frontal gyrus is thought to contribute to higher cognitive functions, such as working memory,\(^{36}\) task-switching,\(^{37}\) and self-focused reappraisal.\(^{38}\) The middle frontal gyrus is important in reorienting attention to an exogenous stimulus\(^ {39} \) and the right inferior frontal gyrus is important for inhibition\(^ {40} \) and hierarchical organization.\(^ {41,42} \) Assuming that both too much and too little are not good, abnormal activity in a certain brain area, regardless of direction, indicates impaired function in that area. Thus, our finding of hypoactivity in the frontal gyrus can be interpreted as indicating that, in the AH group, there may be impaired higher cognitive function, which may, in turn, cause a weakening of top-down control. This suggestion may be supported partially by the finding that the score of the PRMQ retrospective subscale in the AH group was significantly higher than in the non-AH group, indicating greater memory impairment. The anterior cingulate cortex plays a central role in the self-monitoring that is necessary for adaptive goal-directed behavior\(^ {23} \) and in exerting attentional control and selection for action.\(^ {44} \) We observed hypoactivity (decreased glucose metabolism) in the middle cingulate gyrus in the AH group, consistent with other studies.\(^ {13,45} \) Hyperactivity in the cingulate cortex\(^ {15,31,32,46} \) has also been reported. Again, these abnormal activities in the cingulate gyrus/cortex may result in defective self-monitoring, causing impairment in top-down control.

The AH group showed increased activity in the putamen by ROI analysis. In voxel-based analysis, this was ex-
panded to the middle and inferior temporal gyri, fusiform gyrus, and cerebellum. The result of increased activity in the putamen was rather unexpected in that it has classi-
cally been considered to be primarily a motor struc-
ture.47,48) The activation may have been caused by hand
movement in measuring the time duration of AHs.
Arguments against this interpretation are that we observed
bilateral activation of the putamen (although only left put-
tamen in the voxel-based analysis) and some studies re-
ported increased activation in the left caudate nucleus16)
and left basal ganglia,49) and decreased activity in the len-
ticular nucleus.50) in which there was no hand movement
to signal on- and off-set of AHs. An alternative ex-
planation may be that given the role of the putamen in
syntactic processing of sentence comprehension.51) con-
tents of AHs experienced in the AH group may contain
syntactic errors. This needs to be investigated further in fu-
ture studies. We observed significantly higher activation
in the left middle and inferior temporal gyri in the AH
group versus the non-AH group. Increased activity in the
temporal lobe is the finding most frequently and con-
sistently reported, especially in activity studies directly
measuring brain activity occurring during the experience
of hallucinations.29) However, in trait studies that meas-
ured functional activity during auditory stimulation tasks,
decreased activation of the temporal gyrus was ob-
served.52) This seemingly opposite phenomenon has been
called a ’paradoxical effect’.22) suggesting a kind of
’competition for neuronal resources’ between internally
and externally generated neuronal activity. The middle
temporal gyrus is known to be involved in several cogni-
tive processes, including language and semantic memory
processing53) and perceiving inner speech.54,55) The in-
ferior temporal gyrus is associated with visual percep-
tion.56) Thus, our results suggest that internally generated
overrepresentations, stemming from abnormal processing
in language/speech and visual stimuli, may be implicated
in the pathogenesis of AHs. This concept differs from the
previous theories explaining AHs, such as overactivation
of the auditory cortex,57) and misattribution of internally
generated speech,58,59) which all involve the superior tem-
poral gyrus. Taken together, our findings suggest that
overrepresentations or errors in language/speech caused
by hyperactivity in the middle temporal gyrus or putamen
in addition to defective monitoring or top-down control
related to the cingulate gyrus or frontal gyrus may contrib-
ute to the pathophysiology of AHs.

The current study has some limitations. First, there was
no healthy control group, which may limit the inter-
pretation of our findings. However, the comparison be-
tween patients with and without AHs has the advantage of
distinguishing AH-specific neural activities from dis-
 ease-related effects. Second, given that most of the pos-
itive findings disappeared when controlling for confounding
variables, it cannot be ruled out that our findings may be
due to differences in depression, medication doses,
and memory functioning. Third, we could not extend our
positive findings with a threshold of pFWE-corrected and
pFDR-corrected data. Despite these shortcomings,
strengths of the present study are that we recruited homo-
geneous patients meeting the criteria for persistent, prom-
inent, and predominant AHs and included only subjects
experiencing AHs during [18F]FDG uptake period.
Additionally, compared with conventional PET scanners,
the HRRT-PET system used in our study has been reported
to increase the accuracy of the quantification of glucose
metabolism in brain regions due to decreased partial-vol-
ume effects.60) In conclusion, our findings suggest that hy-
poactivity in the frontal and cingulate gyrus, coupled with
hyperactivity in the temporal gyrus and putamen, may
contribute to the pathophysiology of AHs.

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