



Quantitative EEG and low resolution electromagnetic tomography (LORETA) imaging of patients with persistent auditory hallucinations

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Abstract

Electrophysiological studies have demonstrated gamma and beta frequency oscillations in response to auditory stimuli. The purpose of this study was to test whether auditory hallucinations (AH) in schizophrenia patients reflect abnormalities in gamma and beta frequency oscillations and to investigate source generators of these abnormalities. This theory was tested using quantitative electroencephalography (qEEG) and low-resolution electromagnetic tomography (LORETA) source imaging. Twenty-five schizophrenia patients with treatment refractory AH, lasting for at least 2 years, and 23 schizophrenia patients with non-AH (N-AH) in the past 2 years were recruited for the study. Spectral analysis of the qEEG and source imaging of frequency bands of artifact-free 30 s epochs were examined during rest. AH patients showed significantly increased beta 1 and beta 2 frequency amplitude compared with N-AH patients. Gamma and beta (2 and 3) frequencies were significantly correlated in AH but not in N-AH patients. Source imaging revealed significantly increased beta (1 and 2) activity in the left inferior parietal lobule and the left medial frontal gyrus in AH versus N-AH patients. These results imply that AH is reflecting increased beta frequency oscillations with neural generators localized in speech-related areas.

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1. Introduction

Auditory hallucinations (AH) are a relatively common and frequently distressing symptom reported by 50–80% of patients with schizophrenia (Alpert, 1986). Despite a large number of imaging and electrophysiological studies on the origins of AH, the results are not consistent and the substrates of AH remain poorly understood. This paper examined the underlying neural substrates of AH using both quantitative EEG (qEEG) and source localization of neural generators of abnormal qEEG in AH.

Functional neuroimaging studies for schizophrenia patients during AH have revealed activation in speech-related areas such as left superior temporal cortex (Lennox et al., 2000; Suzuki et al., 1993), left inferior parietal cortex (Lennox et al., 2000; Hubl et al., 2004), and left inferior frontal cortex (McGuire et al., 1995). In addition, right superior temporal cortex (Volkow et al., 1987), thalamus (Silbersweig et al., 1995) and cingulate (Cleghorn et al., 1990) activation has been shown during AH. One other study of AH revealed the activation of frontal cortex, amygdala and hippocampus in addition to activation of primary auditory cortex activation (Dierks et al., 1999). These findings suggest AH are a complex feature of psychosis that reflect abnormal activities in multiple interrelated regions.

Although there are several electrophysiological studies of AH in schizophrenia, only a couple addressed the neural genesis of EEG abnormalities during AH. Line et al. (1998) implicated the right temporoparietal area in the genesis of AH through steady state visually evoked potential tomography in eight schizophrenia patients. Ishii et al. (2000) reported a case showing an increased theta rhythm in left superior temporal cortex during AH. More recently, Ropohl et al. (2004) reported increased fast MEG activity (12.5–30 Hz) in the left auditory cortex in a schizophrenia patient who had persistent AH despite taking medication.

Recent studies suggest that gamma (e.g., 30–80 Hz) and beta (e.g., 13–30 Hz) frequency oscillations occur together in the neocortex in response to sensory stimuli over a range of modalities (Barth and MacDonald, 1996; Roelfsema et al., 1997). Gamma oscillations are thought to be involved in feature

binding and association memory (Miltner et al., 1999; Rodriguez et al., 1999; Tallon-Baudry and Bertrand, 1999). Beta 1 (13–20 Hz) oscillations, on the other hand, are the earliest discriminatory response to show enhancement to novel stimuli, preceding changes in the broad-band event-related potential. Gamma and beta oscillations, when they occur together, are thought to represent an activated state of a neuronal network (Haenschel et al., 2000).

Gamma to beta 1 transition in response to novel auditory stimuli has been observed in human electroencephalogram (EEG) (Haenschel et al., 2000) as well as in animal studies (Traub et al., 1999; Whittington et al., 1997). Furthermore, there is evidence of a strong correlation between gamma and beta frequency band in response to novel auditory stimuli (Haenschel et al., 2000; Hong et al., 2004; Traub et al., 1999).

We examined differences between AH versus non-auditory hallucination (N-AH) schizophrenia patients in scalp recorded EEGs in two different ways. First, we utilized qEEG to examine differences in gamma and beta frequencies between schizophrenia patients with and without persistent AH. Secondly, we used low resolution electromagnetic tomography (LOR-ETA; Pascual-Marqui et al., 1994) source imaging to explore the underlying neural generators of abnormal EEG activity. We examined a larger sample of patients with and without persistent AH compared to previous studies. We believe this is the first study to report on the neurogenesis of AH in an Asian population of schizophrenia patients.

We hypothesized that AH patients would show increased gamma and beta power and positive correlations between these two frequency bands. We further hypothesized that LORETA source imaging would show increased activation of speech related areas of brain in AH patients but not N-AH patients.

2. Method

2.1. Subjects

Twenty-five schizophrenia patients with persistent AH lasting for more than 2 years were recruited from the Department of Psychiatry, Inje University Ilsan-

paik Hospital of Korea. Ten of the patients were referred from other hospitals (Korea University Hospital and Koyang City Hospital) through local advertisements. All patients met the DSM-IV criteria (American Psychiatric Association, 1994) for schizophrenia based on both Structured Clinical Interview for DSM-IV (SCID-IV; First et al., 1997), and psychiatric chart review. The diagnosis of schizophrenia was made by the consensus of two board-certified psychiatrists. Twenty-three patients with schizophrenia with N-AH in the past 2 years were also recruited. All AH and N-AH patients were right-handed as assessed by the Neurological Evaluation scale-Korean version (Chae, 1994).

AH status, i.e. experiencing treatment refractory AH for the past 2 years, was determined by the SCID interview and chart histories. To further assess more recent AH status, the hallucinatory behavior subscore from the PANSS (Kay et al., 1987) for the prior two months before testing was examined. As can be seen in Table 1, AH patients showed significantly higher scores on the hallucinatory behavior subscore than N-AH patients.

AH and N-AH patients were group-matched for age, sex, duration of illness, duration on stable medication, number of prior hospitalization and PANSS scores (total, positive and negative score; see Table 1). At the time of enrollment, both groups of patients were all on stable antipsychotic regimens of either risperidone ($N=34$, AH/N-AH=18/16) or olanzapine ($N=14$, AH/N-AH=7/7) without using

any benzodiazepine for at least 2 weeks. None of the patients had a history of central nervous system disease (e.g., epilepsy, cerebrovascular accident), alcohol or drug abuse, electro-convulsive therapy, mental retardation, head injury with loss of consciousness, or hearing impairment. All subjects signed a written informed consent approved by the Inje University Ilsanpaik Hospital Institutional Review Board prior to participation.

2.2. EEG recording

15 min EEGs were recorded from 18 scalp locations (Fp1, F3, C3, P3, Fp2, F4, C4, P4, F7, T3, T5, O1, F8, T4, T6, O2, T1, T2) using the international 10–20 system with a linked ear reference. With the subjects in a relaxed state, EEG was recorded alternatively with eyes closed and open for 1 min each, for a total of 15 min. The recording was carried out with a conventional 32-channel electroencephalograph (Nicolette Biomedical, Madison, WI, USA) in a dimly lit, soundproof, electrically shielded room in Ilsanpaik Hospital. Horizontal eye movements were recorded across electrodes 1 cm lateral to the outer canthus of each eye. The EEG was recorded at a rate of 250 Hz, sensitivity 7 μ V, bandpass filtered at 1–70 Hz. Eye blinking artifacts and segments contaminated by other artifacts on visual inspection were excluded. For analyses, resting EEGs of one artifact-free 30 s epoch from eyes closed were submitted for spectral analysis and LORETA source imaging.

Table 1
Demographic data and PANSS scores of subjects

	AH ($N=25$)		N-AH ($N=23$)		t/χ^2	p
	Mean	S.D.	Mean	S.D.		
Age (year)	39.2	6.8	38.5	7.1	0.62	0.535
Sex (male/female)	11/14		10/13		0.21	0.643
Education (year)	11.4	3.0	13.3	2.2	-2.38	0.022
Duration of illness (year)	8.2	4.2	9.3	4.3	-1.03	0.304
Duration on stable medication (week)	12.3	3.4	13.2	3.2	-0.92	n.s.
Duration of benzodiazepine abstinence (week)	3.5	1.3	3.2	1.1	0.27	n.s.
Number of prior hospitalizations	2.0	2.0	2.7	3.2	0.72	n.s.
PANSS total	54.2	7.9	52.3	8.5	1.96	n.s.
Hallucinatory behavior score	4.2	0.8	0.3	0.4	19.5	0.000
Positive score	28.2	4.9	26.5	3.0	1.40	n.s.
Negative score	27.6	3.1	27.4	3.5	0.25	n.s.

AH, Auditory hallucination; N-AH, no-auditory hallucination; n.s., not significant.

2.3. EEG parameterization

For quantitative EEG analysis, the recorded signals of artifact-free EEG epochs were submitted to spectral analysis using fast Fourier transformation. The square root of absolute power (magnitude), expressed in μV , was computed. The following frequency bands were defined: alpha=8–12, beta 1=13–18, beta 2=19–21, beta 3=22–30, gamma=30–50 Hz. The following electrode sites were averaged together to examine regional effects in each of the separate frequency bands: left anterior (FP1, F7, F3, T1), right anterior (FP2, F8, F4, T2), left posterior (T3, C3, T5, P3, O1), and right posterior (T4, C4, T6, P4, O2).

2.4. Statistical analysis

Group comparisons of demographic data were performed with χ^2 or independent *t*-tests. Group comparisons in spectral power were performed by a repeated-measures ANOVA. Significant main effects and interactions of interest were followed up with independent *t*-tests. Pearson's correlations were calculated between gamma and beta frequency band powers.

Source imaging of AH was made with unpaired *t*-tests of LORETA-Key (Pascual-Marqui et al., 1999) using a Talairach head model. Based on log-transformed power of the estimated electric current density, differences in activity between AH and N-AH patients were assessed by voxel–voxel comparison (Holmes et al., 1996). The 'maximum *t*-statistic', which corrects for multiple comparisons, is reported.

3. Results

The demographic data of AH patients were not different from those of N-AH patients except for degree of education (Table 1). Although there was a significant difference in degree of education between groups, educational level did not correlate with any of the dependent variables in any group ($p > 0.20$ in all cases). Therefore, it appears that EEG band power is unrelated to education levels and was not considered as a significant factor in the EEG and source analyses.

3.1. Quantitative EEG analysis

A 2 (group: AH vs. N-AH) \times 5 (band: alpha, beta 1, beta 2, beta 3, gamma) \times 2 (hemisphere: left vs. right) \times 2 (anterior vs. posterior) repeated-measures ANOVA was performed to examine group differences. There were several significant main effects and interactions. There was no main group effect. Only significant interactions with group will be discussed.

There was a significant interaction between hemisphere and group ($F(1,46)=13.13$, $p < 0.01$) which was largely influenced by a significant group \times band \times hemisphere interaction ($F(4,184)=6.64$, $p < 0.001$). This interaction was due to AH patients showing significantly greater left hemisphere activity in beta 1 in anterior ($t(46)=2.06$, $p < 0.05$) and posterior ($t(46)=2.28$, $p < 0.03$) regions as well as beta 2 activity in anterior ($t(46)=2.36$, $p < 0.03$) regions compared with N-AH patients (Fig. 1). We found significant differences only on beta 1 (13–18 Hz) and beta 2 (19–21 Hz), and previous studies revealed that only early beta frequency (about 10–25 Hz) was involved with gamma to beta transition in response to auditory stimuli (Haenschel et al., 2000; Traub et al., 1999; Whittington et al., 1997). To provide a basis for comparison, mean beta 1 and beta 2 activity from non-psychiatric control subjects ($n=24$) are presented in Fig. 1. This group was not recruited as part of the current study, but consisted of staff at the hospitals from which patients in this study were recruited. As can be seen, N-AH patients and normal controls generated similar mean beta 1 and 2 activity.

For topographical analyses, we combined beta 1 and 2 (13–21 Hz) and presented mean global field power (GFP; Lehmann and Skrandies, 1980) for AH and N-AH patients in Fig. 2. GFP is a measure defined as the standard deviation across multiple channels as a function of time within a sample interval. As can be seen in Fig. 2, AH patients showed greater beta activation in the left anterior and posterior regions compared to N-AH patients.

To examine correlations between gamma and beta power, data across all electrodes were averaged together to generate a grand average band value for each separate band. AH patients revealed significant correlations between gamma and beta powers (gamma and beta 2, $r=.49$, $p < 0.05$; gamma and beta 3, $r=.52$, $p < 0.01$). We also found significant regional correlations (gamma and beta 2; gamma and beta 3) on left anterior ($p < 0.05$), left posterior ($p < 0.01$), and right posterior ($p < 0.05$) except for right anterior region in AH patients. The range of significant correlations was $0.42 < r < 0.61$. N-AH patients did not show any significant correlations between gamma and beta powers.

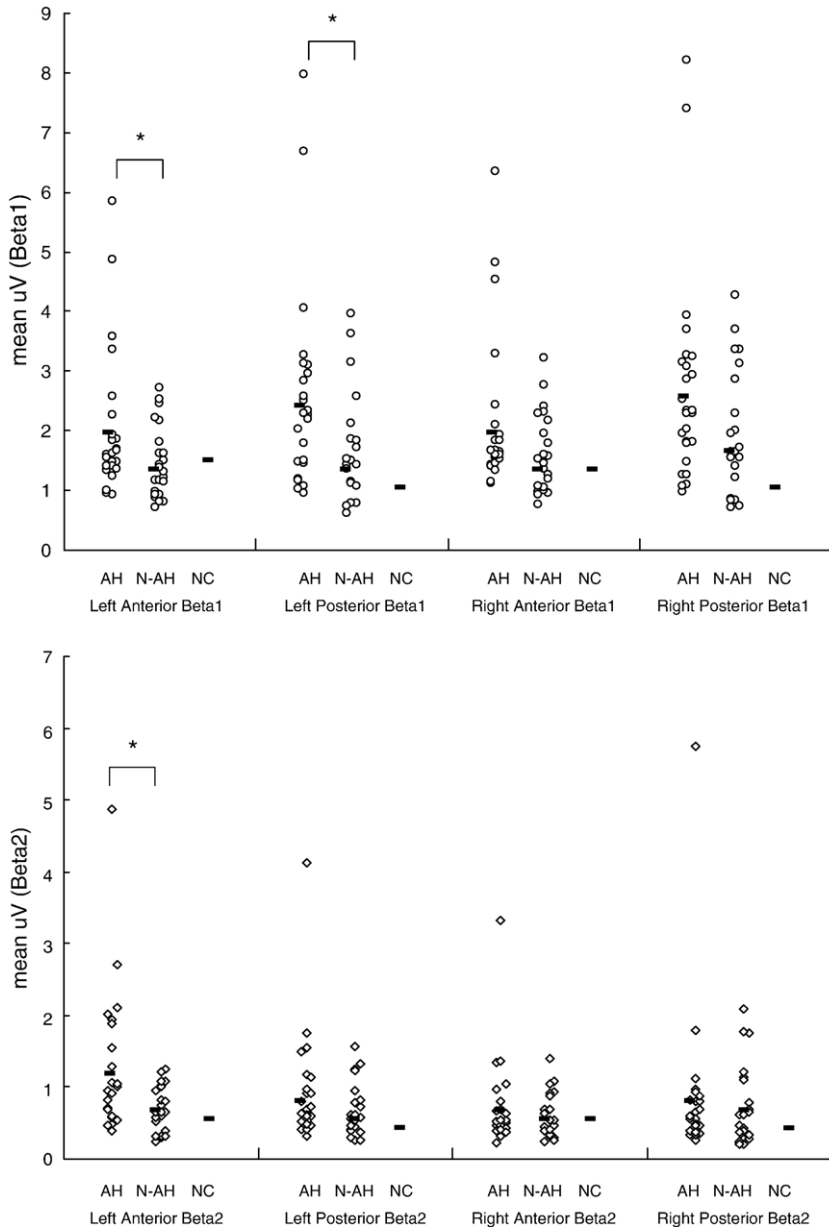


Fig. 1. Scattergrams of regional amplitudes (μV) for beta 1 and 2 activity in auditory hallucination (AH) and non-auditory hallucination (N-AH) patients. Mean beta 1 (top) and 2 (bottom) amplitude for normal control (NC) subjects, indicated by solid horizontal lines, are presented for reference. $*p < 0.05$.

3.2. EEG source analysis

LORETA source imaging revealed a significant increase of beta 1 on Brodmann's area 40 (left inferior parietal

lobule) and beta 2 activity on Brodmann's area 10 (left medial frontal gyrus) in the AH patients compared with N-AH patients ($p < 0.05$) (Fig. 3). There were no other significant group differences in any other band.

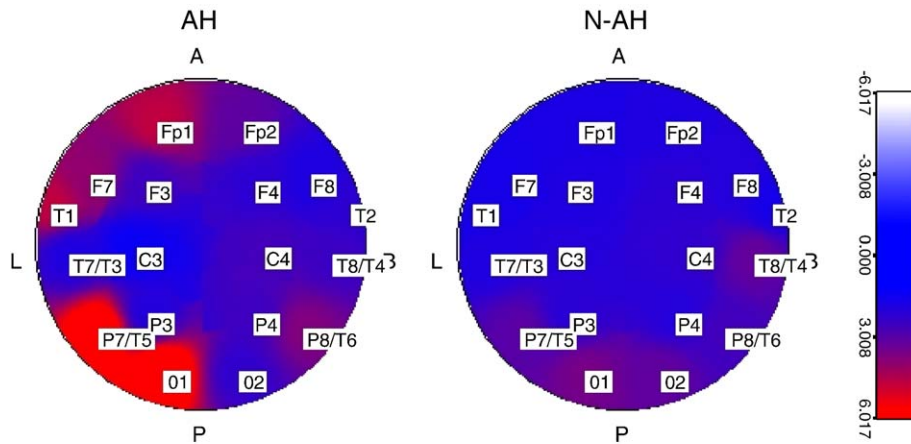
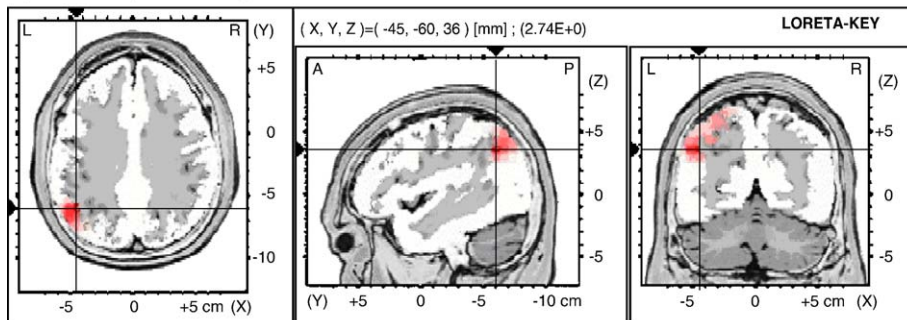


Fig. 2. Maps of mean global field power of beta 1 and 2 (13–21 Hz) in auditory hallucination (AH) and non-auditory hallucination (N-AH) patients. Red color means increased power while blue means decreased power. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

A) Beta 1 (13–18 Hz)



B) Beta 2 (19–21 Hz)

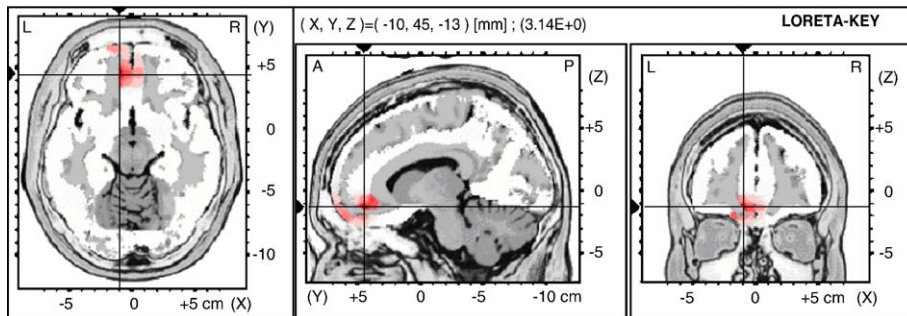


Fig. 3. Current density power analysis between auditory hallucination (AH) and no auditory hallucination (N-AH) patients in beta 1 (13–18 Hz) and beta 2 (19–21 Hz). Displayed are the horizontal (left), sagittal (middle), and coronal (right) sections through the voxel with maximal t -statistic (local maximum). (A) In the beta 1 band, the significant voxel found was best matched to Brodmann's area 40, left inferior parietal lobule, parietal lobe ($p < 0.05$). (B) In the beta 2 band, the significant voxel found was best matched left medial frontal gyrus, frontal lobe ($p < 0.05$).

4. Discussion

Our results show that EEG beta activity is significantly increased in AH patients compared with N-AH patients with source generators located in left medial frontal and left inferior parietal area. Furthermore, we have shown that beta and gamma activity are significantly correlated for patients with persistent AH, consistent with human and animal studies showing relationships between gamma and beta frequency oscillations and auditory processing (Haenschel et al., 2000; Traub et al., 1999). Our results are consistent with previous reports that AH, which is one of the key features of schizophrenia, reflects abnormalities of speech-related areas in their brain.

Beta frequency oscillations have been shown to be generated following periods of synchronous gamma frequency activity (Traub et al., 1999; Whittington et al., 1997). Functionally, the occurrence of subsequent beta oscillations might reflect a modification of neuronal circuitry to encode sensory perception of auditory stimuli (Hong et al., 2004; Kopell et al., 2000; Ropohl et al., 2004). This beta activity has been correlated with the long-range synchronous activity of neocortex during visuomotor reflex activity (Roelfsema et al., 1997), and is able to synchronize over long conduction delays (corresponding to signals traveling a significant distance in the brain) that apparently cannot be tolerated by gamma rhythm (Kopell et al., 2000). In other words, multiple sensory coding can be performed at beta frequencies simultaneously, whereas only local synchronization occurs at gamma frequencies (von Stein et al., 1999). This could be one reason why significant beta activities were found simultaneously in frontal and parietal areas in our study.

Our results also showed that beta 2 and beta 3 activity were positively correlated with gamma activity in AH patients but not N-AH patients. These findings replicate previous studies which revealed strong correlations between gamma and beta frequency oscillations (Haenschel et al., 2000; Hong et al., 2004; Traub et al., 1999) in normal populations. These findings suggest that the brains of AH patients act as if they were experiencing actual auditory stimulation. Significant gamma and beta correlations occurred over the whole cortex except right anterior region.

AH patients showed maximal beta (1 and 2: 12–21 Hz) activity in left temporo-parieto-occipital areas, similar to the findings of Ropohl et al. (2004) (Fig. 2). One strength of the current study was that using LORETA imaging to statistically analyze the sources of AH, greater activity in left inferior parietal lobule (beta 1 band) and left medial frontal gyrus (beta 2 band) were seen in AH patients compared with N-AH patients (Fig. 3). These findings are in line with previous studies indicating dysfunction of left frontal and parietal areas in AH (Frith, 1996; Gaser et al., 2004; Hubl et al., 2004; Lee et al., 2004, 2005; Lennox et al., 2000; McGuire et al., 1995).

Our study replicates and expands upon previous electrophysiological studies using a rather unique sample of schizophrenia patients: 25 schizophrenia patients with persistent AH lasting for more than 2 years and 23 schizophrenia patients without persistent AH. The largest previous electrophysiological study sample included 15 patients, as reported by Havermans et al. (1999). Second, we were able to identify the underlying neural regions associated with long-term AH using source reconstruction techniques that are in line with previous functional imaging studies (Gaser et al., 2004; Hubl et al., 2004; Lennox et al., 2000; McGuire et al., 1995). Finally, we have extended these findings cross-culturally by examining schizophrenia patients consisting solely of Asian participants.

While these results revealed several notable findings, the study had a few limitations. First, only 18 channels were used to record EEG in this study. For more detailed source imaging, examining at least 32 channels would be better. Second, even though our subjects had treatment refractory AH lasting for at least 2 years, we can not be fully sure that hallucinations occurred during the 30 s EEG epochs that were examined. This could be a potential reason for the difference between our results (widespread beta activity in left hemispheric regions in AH patients; Fig. 2) and results of other electrophysiological studies (activity in the left auditory cortex; Ropohl et al. 2004; Ishii et al., 2000) which directly assessed AH state during testing. Future studies will want to consider electrophysiological findings of trait versus state components of AH.

One final limitation is that we did not include normal control participants in this study, as the focus

was on differences between schizophrenia patients with and without AH. It is possible that N-AH patients would show patterns of activation that are functionally different from normal controls. Previous LORETA imaging studies that used drug-naive symptomatic schizophrenia patients revealed that schizophrenia patients showed increased delta activity in fronto-temporal area, and decreased theta and alpha activity in fronto-temporo-limbic area compared with normal controls (Mientus et al., 2002; Pascual-Marqui et al., 1999). Beta frequency bands, which were of primary interest here, showed inconsistent patient versus control differences. Pascual-Marqui et al. (1999) reported increased beta 1, 2, and 3 activities mainly in right temporal areas; however, Mientus et al. (2002) found no significant differences between two groups (only a trend for schizophrenia subjects to show decreased beta (12.5–18 Hz) activity).

Despite these limitations, our study implicated certain key regions as the underlying biological correlates of AH in schizophrenia patients. We can conclude that schizophrenia patients with persistent AH showed increased beta frequency oscillations in their EEG, and its source imaging was located on the left inferior parietal lobule and left medial frontal gyrus which are considered areas relevant to speech processing and production.

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