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Differences in Oscillatory Correlates of Episodic Retrieval in a Virtual Navigation Task between Schizophrenia with and without Hallucinations*

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Neural correlates of episodic memory deficits may be different in schizophrenia patients with hallucinations (SH) and patients without hallucinations (SnH). However, little is known about how specific neural correlates involved in episodic retrieval may differ between SH and SnH. We aimed to determine whether neural oscillations in SH during episodic retrieval are different from those in SnH and normal controls (NC) after navigating rooms in a virtual environment (VE). The VE was used to enhance patient motivation in episodic memory test by engaging higher cognitive involvement. Subjects experienced a navigation session and a retrieval session. Electroencephalogram (EEG) was recorded during the retrieval session, and time-frequency analyses were examined (7 NC, 7 SnH, and 7 SH). Consistent with previous reports, the results revealed that theta power was correlated with successful episodic retrieval, suggesting that the reductions of theta power may contribute to episodic memory deficits in SH and SnH. Notably, the theta power differences between the old and new conditions was positively correlated with episodic retrieval performances across SH, SnH, and NC. Other oscillatory activities (i.e., alpha and beta) may also contribute to episodic retrieval with a diversity of functional relevance across groups. Overall results showed deficits in episodic retrieval, corresponding oscillations in EEG frequency bands. The neural oscillations across different frequencies and their relationship to cognitive processes, including inhibition and attention in episodic memory, are also discussed.

Key words : Episodic memory, Schizophrenia, Hallucination, EEG, Time-frequency analysis, Virtual environment

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Schizophrenia patients have fundamental deficits in episodic memory (Barch & Ceaser, 2012; Kayser, Tenke, Gil, & Bruder, 2009; Kayser et al., 2010; Ranganath, Minzenberg, & Ragland, 2008; Thoma, Zoppelt, Wiebel, & Daum, 2006; Weiss, Goff, Duff, Roffman, & Schacter, 2008). Studies investigating episodic retrieval have suggested that successful episodic memory performance is supported by distinct retrieval processes known as familiarity, i.e., remembering whether an event has occurred, and recollection, i.e., recollecting specific contextual details of that event (Rugg & Curran, 2007; Yonelinas, 2001). Previous studies have shown that episodic memory deficits in schizophrenia patients are caused by deficits in the memory of context (source) rather than of the event itself (Achim & Lepage, 2003; van Erp et al., 2008; Wang, Metzak, Honer, & Woodward, 2010).

Some studies have suggested that these context memory deficits may be specifically linked to the hallucinations (Brebion, David, Bressan, Ohlsen, & Pilowsky, 2009; Brebion, David, Jones, Ohlsen, & Pilowsky, 2007; Brebion, David, Ohlsen, Jones, & Pilowsky, 2007). For instance, schizophrenia patients with hallucinations show self-monitoring errors (Brebion et al., 2000), free-recall intrusion errors (Brebion et al., 2000; Brebion et al., 2009), and deficits in temporal context (Brebion et al., 2007a; Waters et al., 2006a; Waters et al., 2006b) and spatial context memory (Brebion et al., 2007b). Thus, it may be speculated that the neural mechanisms behind episodic memory deficits in schizophrenia patients could be significantly different in those with and without hallucinations. Although few behavioral studies have investigated whether hallucinations are correlated with context memory deficits (Brebion et al., 2009; Brebion, David, Jones, et al., 2007; Brebion, David, Ohlsen, et al., 2007), differences in oscillatory characteristics of contextual memory retrieval between schizophrenia with and without hallucinations were not explored extensively.

A virtual environment (VE) was used to elucidate differences in memory performance between patients with and without hallucinations in this study. Previous research raised the possibility that patients with hallucination may not show a deficit in context memory because of insensitivity of conventional tests. Since tests using VE provides memories of even ts and contexts similar to daily-life episodes (Rizzo et al., 2000; Schultheis, Himelstein, & Rizzo, 2002) and ensure more detailed and immersive experiences to subjects (Freeman, 2008), it may be a useful tool for understanding episodic memory deficits in schizophrenia patients. Moreover, using VE could be particularly advantageous in testing schizophrenia patients

who, in many cases in conventional laboratory tests, appear to experience a lack of motivation.

The present study sought to (1) determine whether abnormal oscillations seen in patients with hallucination were different from those in patients without hallucination during episodic retrieval after experiencing the VE, and (2) discuss the results of oscillations across different frequencies among the 3 groups and their relationship to specific cognitive processes. We employed electroencephalographic (EEG) time-frequency analyses assuming that sophisticated analyses of oscillatory activities would allow for understanding different neural correlates involved in episodic memory retrieval in patients with or without hallucinations and normal controls.

Methods

Subjects Eighteen normal subjects (normal controls: NC) were recruited via a Korea University website posting, advertisements in local newspapers, and flyers. In an initial screening, subjects were excluded if they had any neurological disorder or head injury, any personal history of psychiatric disease, or a family history of psychiatric illness. After the initial screening, potential healthy controls were interviewed using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV Axis II Psychiatric Disorders (First, 1996) and were excluded if they met criteria for any of these disorders.

Eleven schizophrenia patients with persistent auditory hallucination (AH) lasting for more than 2 years (SH) and 11 schizophrenia patients with no hallucination in the past 2 years (SnH) were recruited from the Department of Psychiatry, Inje University, Ilsanpaik Hospital of Korea. All patients met the criteria for schizophrenia based on the Structured Clinical Interview for DSM-IV (SCID-IV; First, 1997). A board-certified psychiatrist evaluated clinical symptoms and conducted chart reviews. AH status, i.e., experiencing treatment-refractory AH in the past 2 years, was determined by clinical interview and chart review. To further assess more recent AH status, the hallucinatory behavior subscore from the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) and Auditory Hallucination Rating Scale (Hoffman et al., 2003) for the 2 months prior to testing were examined. SH and SnH were group-matched for age, sex, duration of illness, duration of stable medication, number of prior hospitalizations, and PANSS scores. At the time of enrollment, all patients were on stable antipsychotic medication (risperidone or olanzapine) with no benzodiazepine use for at least 2 weeks. None of the patients had a history of central nervous system disease (e.g., epilepsy or cerebrovascular accident), alcohol or

drug abuse, electroconvulsive therapy, mental retardation, head injury with loss of consciousness, or hearing impairment. All subjects were right-handed as determined by self-report of the hand used for writing and other precise motor skills.

All subjects gave written informed consent before the experimental procedures commenced, and these procedures were approved by the Ethics Committee of Inje University (IB-0802-006). Data from 6 subjects (1 SH, 1 SnH, 4 NC) were excluded from the analyses because of excessive artifacts. Demographic and clinical data for all of the subjects are summarized in Table 1.

Stimuli and Procedures Subjects received a verbal briefing on the experimental procedures. They were initially assessed with the information and the vocabulary subtests of the Korean Wechsler Adult Intelligence Scale (K-WAIS; Yeom, Park, Oh, Kim, & Lee, 1992) to estimate premorbid IQ.

The navigation program in the VE was developed by the VS TECH Corporation (Bucheon, Korea). As shown in Figure 1A, the VE consists of 4 rooms (office, library, lounge, and conference room) and each room has 15 different typical office appliances (e.g., a vending machine in the lounge). The levels of familiarity, emotional valence, and arousal of these objects were evaluated in a previous study (Hahm et al., 2007). The 3D visual display was presented using a beam projector.

The experiment consisted of a navigation (encoding) session and a retrieval session. In the navigation session, subjects passively navigated the 4 rooms in random order. They were instructed to associate the objects with the rooms in which the objects appeared. Each object was presented for 2000 ms, and the interstimulus interval between the presentations of objects was 5000 ms. In the retrieval session, subjects performed a source recognition test (Figure 1B), which included 40 new and 60 old objects. The old objects were placed at the center of pictures of the rooms where the objects were presented in the navigation session. The new objects were also placed at the center of pictures of the rooms which were randomly allocated to the objects. In the task, subjects were asked to press one button with left hand if the object had been presented during the encoding session in the same room, and press another button with right hand if the object had not been presented during the navigation (counterbalanced across subjects). Each object was presented for 500 ms with randomly varying intertrial intervals (2000-4000 ms).

EEG Recordings Recording, digitization, and subsequent offline data processing were

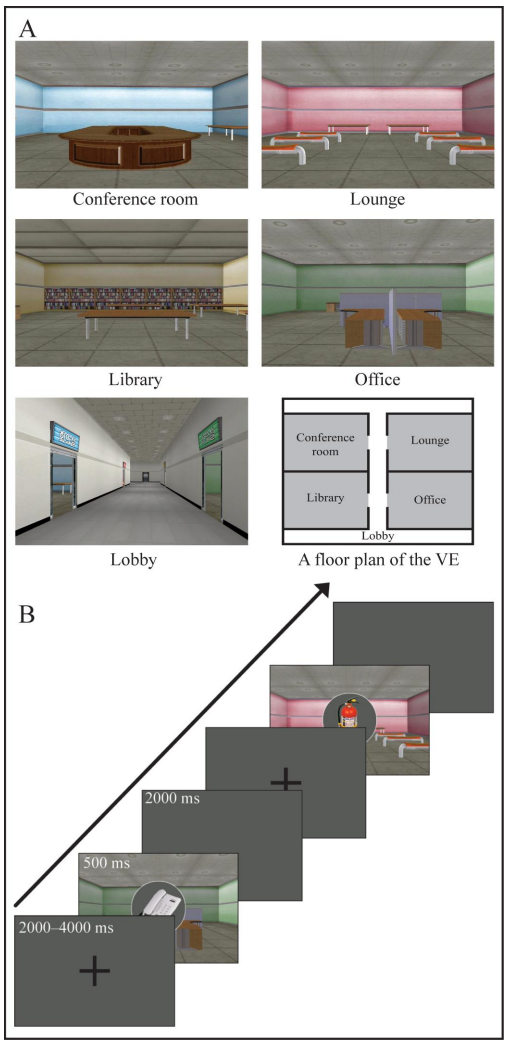

Figure 1. (A) Pictures of the specific rooms and overview of the virtual environment (VE). The VE consists of 4 rooms, i.e., conference room, lounge, library, and office. Each room has 15 different typical office appliances. (B) Schematic depiction of the source recognition test. In the test, subjects were asked to press one button if the object had been presented during the encoding session in the same room, i.e., "old," and press another button if the object had not been presented during navigation, i.e., "new."

carried out with a SynAmps amplifier and Neuroscan (version 4.3) system (Compumedics Neuroscan Inc., El Paso, TX, USA). The EEG was recorded continuously from 64 electrodes by using Quickcap (Compumedics Neuroscan Inc.) according to the extended 10-20 system. The vertical electrooculogram (EOG) was recorded using two electrodes, one located above and one below the right eye. The horizontal EOG was recorded at the outer canthus of each eye. A single ground electrode was placed on the forehead and the reference electrodes were located at both earlobes. The signals were recorded continuously at a sampling rate of 1000 Hz (bandpass filter, 0.05-100 Hz). The electrode impedances were below 10 k Ω.

Oscillatory Power Analyses Gross movement artifacts were removed from the data based on visual inspection. EEG data were digitally filtered with a bandpass of 0.1 - 100 Hz (24 dB/oct, zero-phase shift) and were down-sampled to 500 Hz. The EEG data were corrected for eye movement or blink artifacts by using the regular artifact reduction algorithm implemented in Neuroscan Edit 4.3. The data were epoched between -1000 ms to 2200 ms relative to stimulus onset. The epochs were baseline-corrected, and those containing artifacts larger than ±100 μV were removed. The epochs with correct responses were used for further

analysis. Data from 3 SH and 1 SnH who had less than 20 epochs in either the old or new conditions were excluded (7 SH, 9 SnH, and 14 NC were remained). To match the sample sizes across groups, 7 subjects from SnH and NC groups were randomly selected respectively and subjected to comparative analysis.

Event-related spectral perturbation (ERSP) was computed by Morlet wavelets with increased cycles from 2 cycles (at 2 Hz) to 15 cycles (at 30 Hz) across each epoch, site, and condition. To determine the threshold of significance, bootstrap distributions ($p < .01$) extracted randomly from baseline data (85 points out of 400) and applied 200 times were used (EEGLAB; Delorme & Makeig, 2004). Statistical analyses for ERSP were carried out on the three frequency bands: theta (4 – 8 Hz), alpha (8 – 13 Hz), and beta (13 – 20 Hz). The time-frequency windows used for the analyses were determined based on statistical results: when more than 4 consecutive time windows (i.e., 4 x 50msec = 200 msec intervals) showed significant differences, the windows were clustered and the average value for each ERSP power was obtained. Finally, all significant clusters of time windows were subjected to mixed-model ANOVAs for each time window with condition (2: old and new) as the within-subject factor and group (3: NC, SnH, and SH) as the between-subject factor. Pearson two-tailed correlations analysis between frequency bands and behavioral data were performed to examine whether EEG oscillations reflecting old/new effects were correlated with memory performance of subjects.

Results

Behavior Finally 7 SH, 7 SnH, and 7 NC were enrolled in data analyses. Sociodemographic and clinical data for all of the subjects are summarized in Table 1. All sociodemographic data including the mean age and education levels and premorbid IQ data were not statistically different among the three groups. Clinical characteristics including duration of illness and PANSS score also were not statistically different between the two schizophrenic groups.

Group × Condition ANOVAs were performed on percent of correct response and reaction time (RT). The percent of correct responses in the old condition (M = 61.0, SD = 16.6) was significantly lower than that in the new condition (M = 89.6, SD = 12.3; $F_{(1,18)}=56.36$, $p < .001$). A significant group effect was also found ($F_{(2,18)}=7.55$, $p = .001$). Follow-up comparisons revealed that the SH group had a lower percentage of correct responses (M = 63.2, SD = 11.3) as compared to the NC group (M = 83.5, SE =3.4 for NC, $p = .004$). No effect of group × condition interaction

Table 1. Sociodemographic and clinical characteristics of schizophrenia and healthy control subjects (M and SD)

	SH (n = 7)	SnH (n = 7)	NC (n = 7)	*F*	*p*
Age (years)	33.86 (9.89)	35.29 (13.19)	28.86 (4.56)	.82	.46
Sex (M/F)	2/5	4/3	3/4		
Education level (years)	13.43 (1.90)	13.57 (2.70)	15.71 (1.80)	2.42	.12
Duration of illness (years)	7.14 (3.90)	4.85 (3.64)	-	.19	.30
Premorbid IQ (WAIS)					
Information	8.83 (2.32)	9.29 (4.23)	9.57 (2.64)	.09	.92
Vocabulary	9.83 (1.47)	8.86 (3.81)	11.57 (2.23)	1.76	.20
Global symptom score (PANSS)					
Positive	20.71 (5.47)	17.00 (9.85)	-	.76	.40
Negative	18.43 (4.54)	18.00 (7.51)	-	.02	.90
General	35.71 (7.20)	34.43 (11.01)	-	.07	.80
Auditory hallucination score	21.57 (5.65)	-	-		

Note: SH, Schizophrenia with Hallucination; SnH, Schizophrenia without Hallucination; NC, Normal Control; PANSS, Positive and Negative Syndrome Scales; WAIS, Wechsler Adult Intelligence Scale

($F_{(2,18)}$=0.59, p =.563) was found. For the RT, a significant main effect of condition indicated that all subjects responded faster in the new (M = 1093.5 ms, SD = 182.9) as compared to the old condition (M = 1338.9 ms, SD = 285.7; $F_{(2,18)}$=15.41, p =.001). No main effect of group ($F_{(2,18)}$=.51, p =.692) or group × condition interaction ($F_{(2,18)}$=1.17, p =.333) was found.

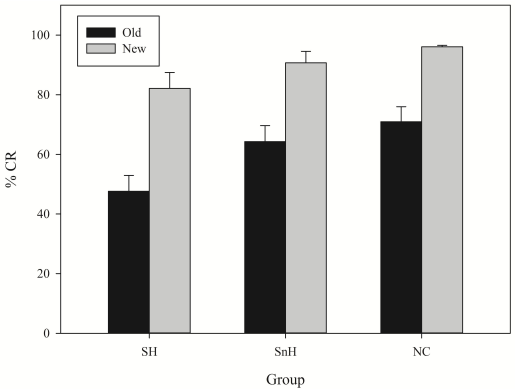

Figure 2. (A) The percent of correct responses for the old and new conditions for NC, SnH, and SH. SH group had a lower percentage of correct response as compared to the NC group.

Theta Frequency Band (4-8 Hz) Two separate 3 × 2 mixed-model ANOVAs with the factors group and condition were performed on a frontal (Fz) theta power in a mid-time window

from 800 to 1100 ms and in a late-time window from 1250 to 1450 ms. As illustrated in Figure 3A, the theta old/new effect was characterized by stronger frontal theta power for the old condition as compared to the new condition in the mid-time window ($F_{(1,18)}$=6.47, p = .020). Although visual inspection of Figure 3A indicates theta power differences among normal and schizophrenia patient groups, no statistically significant main effect of group ($F_{(2,18)}$=0.86, p = .439) or group × condition interaction ($F_{(2,18)}$=3.00, p = .075) was found. However, when the groups of schizophrenia patients were combined and compared to the NC group, a significant group × condition interaction ($F_{(1,19)}$=4.40, p = .050) as well as a

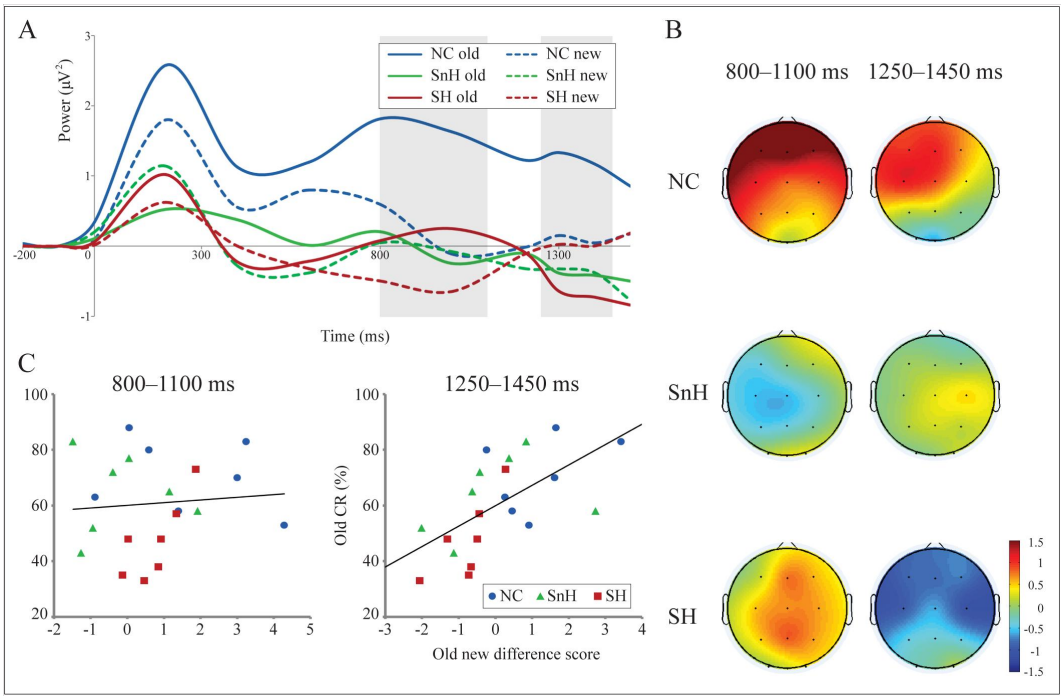

Figure 3. (A) Average theta power time course for the old and new conditions at Fz for NC, SnH, and SH. The gray-shaded areas correspond to the mid-time window (800 to 1100 ms) and the late-time window (1250 to 1450 ms), respectively. (B) Topographic maps of theta power differences between the old and new conditions in the mid-time window (left) and late-time window (right). (C) Relationship between theta power differences between the old and new conditions at Fz and percentage of correct responses for the old condition in the mid-time window (left) and the late-time window (right). In the late-time window, the theta power difference between the old and new conditions at Fz was positively correlated with recognition memory accuracy in subjects across all 3 groups.

main effect of condition ($F_{(1,19)}$=9.41, p = .006) were observed. These results indicate that schizophrenia patients showed reduced theta power in the retrieval of the previously encoded old stimuli as compared to NC.

For the late-time window (Figure 3A), a significant interaction of group × condition was observed ($F_{(2,18)}$ = 4.52, p = .026). Pairwise comparisons confirmed significant differences between NC and SnH ($t_{(12)}$ = 2.26, p = .043) and marginally significant differences between NC and SH ($t_{(12)}$ = 2.06, p = .061) in the theta power for the old condition, whereas the theta power was similar across groups for the new condition. These results indicate that the 3 groups showed different theta activity in the retrieval of the previously encoded old stimuli in this time window. No significant main effect of group ($F_{(2,18)}$ = 1.04, p = .374) or condition was observed ($F_{(1,18)}$ = 0.19, p = .668).

Alpha Frequency Band (8-13 Hz)

Alpha suppression was topographically widespread, but maximally decreased alpha power was observed in the posterior area. As illustrated in Figure 4A, the alpha power decrease became pronounced about 200 ms after stimulus onset and was prolonged in the NC group. However, similar patterns of the alpha power decrease were not observed in the SH group. Poor development of alpha power decrease and disappearance in the relatively early time window were characteristic of both the old and new conditions in the SH group. Consistent with this observation, the alpha suppression from 1050 to 1450 ms after stimulus onset at Oz showed a significant group effect ($F_{(2,18)}$ = 5.68, p = .012). *Post hoc* comparisons showed that the SH group (M = .50, SD = .71 for old; M = 1.17, SD = 1.05 for new) had a lower level of alpha suppression as compared to the NC group (M = -2.81, SD = 2.91 for old; M = -2.73, SD = 3.39 for new; p = .010). Alpha suppression was significantly stronger for the old condition as compared to the new condition from 1050 to 1250 ms ($F_{(1,18)}$ = 6.89, p = .017). However, separate repeated-measures ANOVAs on alpha power for the 3 groups indicated only the SnH group showed greater alpha suppression in the old condition than in the new condition ($F_{(1,6)}$ = 15.25, p = .008).

Beta Frequency Band (13-20 Hz)

Oscillatory beta power analyses are illustrated in Figure 4B. In the time window ranging from 800 to 1400 ms, only the SH group showed exaggerated beta activities in both the old and new conditions, with the maximal power increase at posterior sites ($F_{(2,18)}$ = 7.68, p = .004). *Post hoc* comparisons revealed that the SH group (M = 1.44, SD = 1.27 for old; M = 1.40, SD = 1.10 for new) showed a significantly enhanced

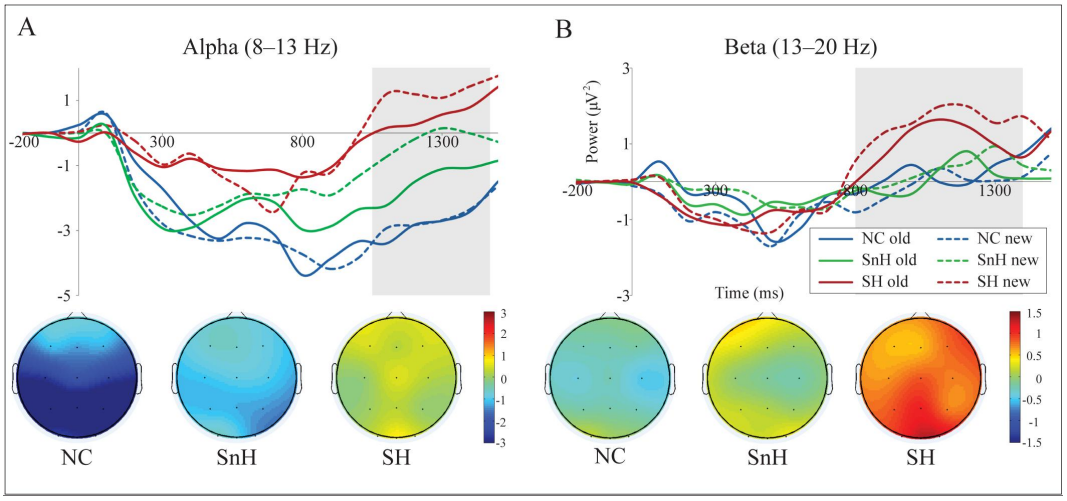

Figure 4. (A) Average alpha power time course for the old and new conditions at Oz (upper) and topographic maps for alpha power (lower) from 1050 to 1450 ms after stimulus onset for NC, SnH and SH. Alpha suppression was not only quantitatively pronounced but also prolonged in widespread cortical regions in both the NC and SnH groups but not in the SH group. (B) Average beta power time course for the old and new conditions at Oz (upper) and topographic maps for beta power (lower) from 800 to 1400 ms after stimulus onset. Only the SH group showed exaggerated beta power in both the old and new conditions.

beta power compared to the NC (M = .20, SD = .47 for old; M = .25, SD = .97 for new; p = .006) and SnH (M = -.06, SD = .61 for old; M = .07, SD = .40 for new; p = .019) groups. These results suggest that the exaggerated beta power at posterior sites could be related to one of several possible neural correlates of hallucinations. No significant condition main effect ($F_{(1,18)}$ =. 02, p = .822) or condition × group interaction ($F_{(2,18)}$ = .06, p = .940) was observed.

Correlation between Frequency Bands and Behavior Based on our results reporting main effect of condition or group × condition interaction, we examined whether EEG oscillations reflecting the old/new effects were correlated with memory performance of subjects in the 3 groups. Pearson two-tailed correlation analyses between percentage of correct responses and the old/new differences of the mid-theta activity during 800 – 1100 ms at Fz, the late-theta activity during 1250 – 1450 ms at Fz, and the alpha activity during 1050 – 1250 ms at Oz, were performed. Magnitudes of the old/new effects of the mid-theta activity at Fz as well as the alpha activity at Oz were not correlated with recognition memory performance

(r = .083, p = .720 and r = .013, p = .957, respectively). Importantly, however, during the late-theta activity from 1250 to 1450 ms, the theta power difference between the old and new conditions at Fz was positively correlated with recognition memory accuracy in subjects across the 3 groups (r = .500, p = .021). When considering RT, brain oscillations in this late-time window reflect the retrieval process for the old stimuli rather than for the new stimuli, since responses for the new stimuli had already been completed for all 3 groups. Consistent with this behavioral RT data, correlation analysis on percentage of correct response on the old stimuli revealed that subjects who showed the larger late-theta old/new effects also had a higher percentage of correct responses for the old stimuli (r = .627, p = .002; Figure. 3C), whereas the late-theta old/new effects and percentage of correct response on the new stimuli were not correlated (r = -.006, p = .980). The results suggest that, across subjects, the late-theta activity reflects cognitive processes that may contribute to successful memory retrieval for the previously encoded episodic information.

Discussion

This study investigated characteristic EEG oscillatory activities and ERPs in episodic retrieval in healthy controls and schizophrenia patients with and without hallucinations by using an episodic memory task in a VE. One main finding of the study is that SH patients had a significantly lower percentage of correct responses as compared to the other 2 groups in tests of episodic retrieval. Table 2 present a summary of time-frequency analyses. An elaboration of the impact of the various oscillatory characteristics across EEG bands on the behavioral performances of the 3 groups follows.

Table 2. Summary of time-frequency analyses across EEG bands

Band	Time window (msec)	Site	Group comparisons
Theta 1 (4-8 Hz)	800-1100	Frontal	NC > SnH and SH
Theta 2 (4-8 Hz)	1250-1450	Frontal	NC > SnH ≒ SH for old
			NC ≒ SnH ≒ SH for new
Alpha (8-13 Hz)	1050-1450	Occipital	NC ≒ SnH < SH
Beta (13-20 Hz)	800-1400	Occipital	NC ≒ SnH < SH

Note: SH, Schizophrenia with Hallucination; SnH, Schizophrenia without Hallucination; NC, Normal Control

Theta Power and Episodic Retrieval

The present results demonstrate that patients in the SH and SnH groups did not show the theta old/new effect in the mid-time window (800 to 1100 ms), whereas NC showed greater theta power for the old than the new stimuli. These results are consistent with previous reports that have demonstrated that increased theta power is correlated with successful episodic retrieval (Jacobs, Hwang, Curran, & Kahana, 2006; Klimesch, 1999; Klimesch et al., 2001; Osipova et al., 2006) and the reduction of theta power may contribute to episodic memory deficits in schizophrenia patients. Notably, the magnitude of the theta power difference between the old and new conditions in the late-time window(1250 to 1450ms) was correlated with accuracy in recognition memory across the subjects. These results suggest that the theta activity in this late-time window, could be directly related to retrieval performance for the previously encoded old stimuli. Furthermore, this suggestion is supported by the findings in our results that EEG oscillations in other time windows or in other frequency bands showing the old/new effects were not significantly correlated with the retrieval performance.

To the best of our knowledge, our study is the first to provide direct evidence for the positive correlation between retrieval performance and theta activity across SH, SnH, and NC groups. The precise functional relationship between memory retrieval and theta activity in the late-time window is not yet clearly delineated, but our results suggest several possibilities that can be tested in further investigations. One possibility is that the lack of increase in theta activity in the late-time window in schizophrenia patients might reflect a deficit in the inhibitory function that suppresses interfering information in episodic retrieval. In a previous study, Staudigl, Hanslmayr, and Bauml (2010) examined retrieval-induced forgetting, in which retrieving a subset of previously studied material can cause subsequent forgetting of related nonretrieved material (Spitzer, Hanslmayr, Opitz, Mecklinger, & Bauml, 2009). The authors suggested that theta activity could arise because of inhibition of competing memory traces and serve as a neural marker of the dynamics of interference in episodic retrieval. Moreover, the theta activity at frontal sites that reflects the dynamics of interference was observed lately in the time course of theta power (i.e., 1200 to 1800 ms Waldhauser, Johansson, & Hanslmayr, 2012). Consistent with these results, our results indicate that similar dynamics of theta activity governing episodic retrieval could appear over a prolonged latency in the time course of theta power in NC, but not in SH and SnH.

A second possibility is that the lack of increase in the theta activity and lowered

memory performance might be due to deficits in contextual memory processing in schizophrenia patients, especially those with hallucinations. Cognitive models of recognition memory (Wixted, 2007) have distinguished between recollection-based recognition versus familiarity-based recognition (Duzel, Penny, & Burgess, 2010). There is much evidence that theta activity are associated with recollection-related retrieval process (Gruber, Tsivilis, Giabbiconi, & Muller, 2008; Guderian & Duzel, 2005; Klimesch et al., 2001) and may play a key role in coordinating the neural activities of long-range interactions in the brain required during recollection(Barbeau et al., 2005; Sirota et al., 2008). Moreover, the time course of the late-theta effect in this study is in agreement with that of recollection-based ERP components in previous ERP studies (Klimesch et al., 2001).

Impairment of Alpha Suppression in SH Previous studies have consistently reported abnormalities in the alpha power in schizophrenia patients during both in the resting state (Sponheim, Clementz, Iacono, & Beiser, 1994; Uhlhaas, Haenschel, Nikolic, & Singer, 2008) and in various experimental tasks (Basar-Eroglu, Schmiedt-Fehr, Marbach, Brand, & Mathes, 2008; Haenschel et al., 2009). In the present study, alpha suppression was not only quantitatively pronounced, but also prolonged, in widespread cortical regions in both the NC and SnH groups after stimulus onset. Only the SH group lacked these characteristics of alpha suppression, suggesting that the lack of alpha suppression in SH could be associated with hallucination. Thus far, few research studies have been published on whether the characteristics of alpha suppression could be categorized in schizophrenia subgroups according to the presence or absence of hallucinations. However, the extent of alpha suppression is known to depend on the tonic power measured during a reference interval or a baseline resting condition (Klimesch, Doppelmayr, Schwaiger, Auinger, & Winkler, 1999; Klimesch, Sauseng, & Hanslmayr, 2007). Previous research with schizophrenia patients has reliably shown decreased alpha power in resting EEG (Klimesch et al., 1999; Sponheim et al., 1994), and this deficit is associated with increased deviance in brain morphology, including the enlargement of the third ventricle (Sponheim, Clementz, Iacono, & Beiser, 2000) and reduction in thalamic volume (Gur et al., 1998) and metabolism (Buchsbaum et al., 1996). Therefore, the lack of alpha suppression observed in our results may simply reflect more severe abnormalities in the resting EEG of schizophrenia patients with hallucination than in those without hallucination.

Our results also raise another possibility that

the difference in alpha suppression between schizophrenia subgroups reflects different levels of attention between patients with and without hallucination. It has been well-documented that lower alpha, especially in the range of 6 – 10 Hz, likely reflects unspecific processing demands such as attention (Klimesch, 1999; Klimesch, Doppelmayr, Pachinger, & Russegger, 1997; Klimesch, Doppelmayr, Russegger, Pachinger, & Schwaiger, 1998). Hence, our results may reflect a possible attention deficit in episodic retrieval in the SH group because the lack of alpha suppression is significantly pronounced during 1050-1450 ms time period after stimulus onset in this group. However, further investigation is necessary to firmly establish whether the lack of alpha suppression in schizophrenia patients is associated with hallucinations.

Exaggerated Beta in SH Compared to the other groups, only schizophrenia patients with hallucination showed significantly enhanced beta power, suggesting that the exaggerated beta power could be a representation of oscillatory activity associated with hallucination. Consistent with our results, another study found that the positive symptoms of schizophrenia patients were correlated with enhanced beta activity and that this association was particularly robust in the presence of auditory and visual hallucinations (Lee et al., 2006). However, most of the previous studies have reported enhanced beta activity during the resting state, not event-related state, in patients both with and without hallucinations (Venables, Bernat, & Sponheim, 2009). More research is required to provide direct evidence for a relationship between beta activity in stimulus-evoked states and hallucination.

Another explanation can be inferred from studies in Parkinson 's disease (PD) that chronic disruption of dopamine transmission in PD is associated with exaggerated beta activities (Jenkinson & Brown, 2011; Mallet et al., 2008). Dopamine is also a neuromodulator that has traditionally been implicated in the pathophysiology of schizophrenia (Uhlhaas & Singer, 2010). Our results showing exaggerated beta activity might have implications for the pathophysiology of schizophrenia. It is possible that patients with hallucination in our study, who are under the effect of antipsychotics, might have a chronic disruption of dopamine transmission accompanying abnormally enhanced beta activities. Future studies need to elucidate a direct impact of the disruption of dopaminergic transmission on event-related oscillations in schizophrenia patients with hallucinations.

Conclusions The present experiment using a VE revealed that SH showed a deficit in episodic retrieval and that corresponding

oscillations in EEG frequency bands were different from SnH and NC. The findings are consistent with results of previous investigations that theta activities were directly correlated with episodic retrieval (Jacobs et al., 2006; Klimesch, 1999; Klimesch et al., 2001; Osipova et al., 2006). Moreover, the different oscillatory activities (i.e., alpha and beta) were also associated with episodic retrieval with diverse functional relevance.

Our conclusions are limited by the fact that the small number of subjects from whom the conclusions were derived. Future research should be carried out on a larger number of subjects. Third limitation was the item proportions were biased towards old items (60 old and 40 new items) in the source recognition test. The 3D navigation program was pre-made so that a user can not be allowed to change the details of stimuli presentation. Equal proportions of old and new items would be a better task design.

The findings of our study have implications for future studies of neural mechanisms of episodic memory in schizophrenia patients. Firstly, although several studies have investigated neural activities correlated with symptoms of schizophrenia patients (Lee et al., 2006; Merrin & Floyd, 1992), many studies have categorized schizophrenia patients with different symptoms as a unitary group when investigating the neural correlates of various memory functions. Using time-frequency analyses, we showed that patients with or without hallucination have different characteristics in neural oscillations across different frequencies in episodic retrieval. Secondly, the episodic memory test using VE in our study includes perceptual details of objects, spatiotemporal contextual elements, and binds the different types of information together for memory retrieval (Plancher, Tirard, Gyselinck, Nicolas, & Piolino, 2012). Studies using VE can provide more realistic and immersive experiences for patients with decreased motivation, more so than conventional tests, and ensure more sophisticated understanding of the neural mechanisms of schizophrenia with various symptoms, including hallucinations.

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가상환경을 이용한 일화기억 인출에서 조현병 환청군과 비환청군의 신경 진동의 차이

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환각은 조현병에서 나타나는 대표적인 정적 증상으로 일화 기억의 인출과 관련되어 있다는 행동 연구들이 소개되었다. 그러나, 환각이 있는 조현병과 없는 조현병 환자에서 나타나는 일화기억의 결손의 신경 기전이 어떻게 다른지에 대해서는 알려진 바가 적다. 본 연구는 시간-주파수 분석을 이용하여 조현병 환청군과 비환청군에서 일화 기억을 인출할 때 나타나는 신경학적 기전을 비교하였다. 7명의 조현병 환청군, 7명의 비환청군, 그리고 7명의 정상군 피험자가 4개의 방으로 구성된 가상의 공간을 탐색하면서 어떤 물건을 어느 방에서 보았는지를 학습한 후, 인출과제를 시행하는 동안 뇌파를 측정하였다. 피험자는 맥락과 물건의 짝이 학습 시와 동일한 경우(“old” 조건)와 학습 시 맥락에서 물건을 본 적이 없는 경우(“new” 조건)에 대해 각각 다른 버튼을 누르도록 지시 받았다. 행동결과로 환청군은 비환청군과 정상군에 비해서 old 조건에서의 인출정확도가 유의하게 낮은 반면, new 조건에서는 세 집단의 인출정확도가 다르지 않았다. 뇌파에 대한 시간-주파수 분석 결과, 세타의 활동 감소가 정상군과 다르게 환청군과 비환청군에서 관찰되었으며, 조건 간 세타파워의 차이는 정확반응율과 높은 상관을 나타냈다. 이러한 결과는 세타 활동이 성공적인 일화기억의 인출과 관련되어 있음을 시사한다. 환청군에서는 특징적으로 알파 억제의 감소와 베타의 증가가 나타났는데, 환청군의 뇌파 특성과 일화기억 인출 결손의 기능적 관련성을 시사한다. 다양한 주파수대역의 신경 진동과 관련된 인지적 과정에 대해 광범위하게 논의하였다.

주제어 : 일화기억, 조현병, 환각, 뇌파, 시간-주파수 분석, 가상환경