Schizophrenia Research xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Differences in central serotoninergic transmission among patients with recent onset, sub-chronic, and chronic schizophrenia as assessed by the loudness dependence of auditory evoked potentials

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ARTICLE INFO

Article history:
Received 12 March 2015
Received in revised form 15 July 2015
Accepted 19 July 2015
Available online xxxx

Keywords:
LDAEP
Serotonin
Schizophrenia
Auditory processing

ABSTRACT

Previous research has shown that abnormalities in serotonin systems are associated with schizophrenia. The loudness dependence of auditory evoked potentials (LDAEP) has been used as a metric of central serotonin activity. The present study aimed to evaluate LDAEP in patients with schizophrenia of differing chronicity. Sixty-four patients with schizophrenia and 50 healthy controls were enrolled in this study. LDAEP and psychometric ratings, such as the positive and negative syndrome scale (PANSS), were measured. The cohort was stratified into three subgroups according to the duration of illness: recent onset (<2 years, n = 21), sub-chronic (2–9 years, n = 28), and chronic (≥10 years, n = 15) groups. The LDAEP differed significantly among the three groups. A post-hoc analysis (Bonferroni) demonstrated that the LDAEP differed significantly between the recent onset and chronic groups ($p = 0.029$), and between the healthy control and chronic groups ($p = 0.008$). Age, sex, dosage of antipsychotics, and smoking did not significantly affect the group differences. In the correlation analysis, there was a significant correlation of LDAEP values with illness duration ($r = -0.259$, $p = 0.045$). The present study verifies that the LDAEP is related to the duration of illness in patients with schizophrenia. This suggests that central serotonin neurotransmission is changeable, and it may depend on the chronicity of schizophrenia pathology.

1. Introduction

The pathophysiology of schizophrenia is not clear. However, previous research has suggested that abnormalities in serotonin (5-HT) systems are associated with schizophrenia. Some studies have suggested that the serotonergic hallucinogens, including lysergic acid diethylamide (LSD), induce psychotic features (Aghajanian and Marek, 2000). Another study reported that 5-HT2A agonists worsen the symptoms of schizophrenia (Santini et al., 2013). Conversely, 5-HT2A antagonists, for example atypical antipsychotics, have been used as a treatment for schizophrenia (Meltzer, 1999). The 5-HT1A receptor, serving as an inhibitory autoreceptor, has been implicated in the pathophysiology of schizophrenia through postmortem studies; these studies have reported increased 5-HT1A density in several brain regions in patients with schizophrenia (Burnet et al., 1997; Gurevich and Joyce, 1997; Simpson et al., 1996; Sumiyoshi et al., 1996; Tauscher et al., 2002). However, no differences (Frankle et al., 2006) and decreased binding (Yasuno et al., 2004) have also been reported.

Recently, serotonergic activity was measured in patients with schizophrenia using the loudness dependence of auditory evoked potentials (LDAEP), which is a non-invasive event-related potential (ERP) method (Juckel, 2015). Preclinical/animal research has indicated that the LDAEP is a reliable indicator of central serotonergic activity (Juckel et al., 1997). Genetic studies have shown that the LDAEP was significantly related to 5-HT control genes (Juckel et al., 2010; Park et al., 2013). The LDAEP has been identified as being inversely associated with central serotonergic activity, with a large LDAEP reflecting low serotonergic neurotransmission and vice versa. Juckel and colleagues first reported the relationship between LDAEP and schizophrenia (Juckel et al., 2003, 2008). They found that after treatment with 5-HT2 antagonists, the LDAEP tended to increase, indicating normalization of serotonergic function in the patients with schizophrenia (Juckel et al., 2003). Another study also found that the LDAEP was significantly lower in patients with schizophrenia than in healthy controls (Park et al., 2010). Furthermore, Gudlowski et al. (2009) found that serotonergic activity had already increased (low LDAEP) before the onset of the full-blown psychosis of schizophrenia and remained enhanced for the further

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http://dx.doi.org/10.1016/j.schres.2015.07.036
0920-9964/

course of the disease. However, these results have not been replicated. In contrast with previous studies, some authors (Wyss et al., 2013) have reported that patients with schizophrenia showed a significantly higher LDAEP in both hemispheres compared with controls. However, this study did not consider the duration of illness and was conducted with a relatively small number of participants.

Taken together, the findings of 5-HT activity and the LDAEP in patients with schizophrenia are still unclear. Thus, the present study aimed to determine whether the LDAEP is different according to the phase of the disease, such as recent onset or chronic periods, in patients with schizophrenia, and whether there is a relationship between the LDAEP and clinical characteristics of patients with schizophrenia.

2. Materials and methods

2.1. Participants

Sixty-four patients with schizophrenia (34 women) were enrolled. The patients had been diagnosed according to the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I Psychiatric Disorders (First et al., 1997). All patients were on stable doses of atypical antipsychotic medications. Patients with significant comorbid neurological illness, mental retardation, substance abuse, and other major psychiatric disorders were excluded. In addition, patients receiving antidepressants were excluded.

Fifty healthy controls (25 women) were recruited from the local community, through advertisements in local newspapers and posters. They were initially screened for any indicators that might have affected the experiment (e.g. hearing loss, low education levels, and severe medical illness). After initial screening, controls were interviewed and subsequently excluded if they had any personal or family history of psychiatric illnesses.

Informed consent was obtained from all participants before beginning the investigation. The study protocol was approved by the Institutional Review Board of Inje University.

2.2. Design

Auditory processing for the LDAEP was measured at a single time point (i.e., in a cross-sectional design). Demographic and clinical data were obtained, and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was completed by the investigators. Patients with schizophrenia were stratified into three subgroups according to the duration of illness: recent onset (<2 years), sub-chronic (2–9 years), and chronic (≥10 years). Recent onset schizophrenia was defined as a recent onset of psychotic illness, with the beginning of the first major psychotic episode (characterized by psychotic symptoms lasting at least 2 weeks) occurring within the last 2 years (Karlsgodt et al., 2008; van Haren et al., 2003).

2.3. EEG acquisition and preprocessing

Each participant was seated in a chair in a sound-attenuated room. The auditory stimulation was comprised 1000 stimuli with a randomized interstimulus interval of 500 to 900 ms. Tones of 1000 Hz and 80 ms duration (with 10 ms rise and fall times) were generated by the E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA) and presented at five intensities (55, 65, 75, 85, and 95 dB SPL) via headphones (MDR-D777, Sony, Tokyo, Japan). Electroencephalograms were amplified and recorded using a NeuroScan SynAmps2 amplifier (Compumedics USA, El Paso, TX, USA). EEG data were recorded from 64 scalp sites using QuikCap (Compumedics USA, El Paso, TX, USA) with two additional bipolar electrodes to record the vertical and horizontal electrooculograms. The signals were referenced to both mastoid and grounded at AFz electrode. Impedances were maintained below 5 kΩ for all electrodes. Data were collected at a sampling rate of 1000 Hz, using a bandpass filter of 0.1–100 Hz.

Data were reanalyzed using Scan 4.3 software with a bandpass filter of 0.1–30 Hz, and ocular contamination was removed using standard blink-correction algorithms (Semlitsch et al., 1986). Event-related potential sweeps with artifacts exceeding 70 μV were rejected at all electrode sites. For each intensity and for each subject, the N1 peak (negative-most amplitude between 80 and 130 ms after the stimulus) and P2 peak (positive-most peak between 130 and 230 ms after the stimulus) were then determined at the Cz electrode. The peak-to-peak N1/P2 amplitudes were calculated for the five stimulus intensities, and the LDAEP was calculated as the slope of the linear-regression curve. The Cz electrode was chosen because previous studies have shown this to be a reliable site at which the amplitude is higher than at other electrode sites (Gudlowski et al., 2009; Park et al., 2010, 2011; Park and Lee, 2013). In addition, quality control was conducted periodically, such as checking the stimulus intensity (every week) and the impedance of the electrical cap (every day).

2.4. Statistical analysis

The demographic, psychopathological, and biological measures of the groups were compared with an ANOVA, post-hoc analysis (Least Significant Difference: LSD), Student's t-test, chi-square tests, Pearson's correlation, and Pearson's partial correlation using SAS 9.3 and SALT 2.5 version software. All tests were two-tailed, and group differences were tested at the $p < 0.05$ level.

3. Results

Patients were categorized as having recent onset (n = 21), sub-chronic (n = 28), chronic (n = 15) schizophrenia. ERP waveforms for each group were presented with separate waves for each loudness level (Fig. 1). The demographic data and scores of the PANSS are presented in Table 1. There were no significant differences among any of the variables. The LDAEP at the Cz differed significantly among the recent onset, sub-chronic, chronic groups, and healthy controls (0.97 ± 0.66 vs. 0.77 ± 0.58 vs. 0.50 ± 0.68 vs. 1.00 ± 0.61 μV, respectively; $F(3, 113) = 2.850$, $p = 0.041$) (Fig. 2, left). A post-hoc analysis revealed that the LDAEP differed significantly between the recent onset and chronic groups ($p = 0.029$), and between the healthy control and chronic groups ($p = 0.008$). Controlling age, dosage of antipsychotics, as well as sex, and smoking (Min et al., 2012) as covariates did not significantly change the results. The LDAEP values between healthy controls and patients with schizophrenia (all the patients combined) showed a significant trend of difference ($p = 0.061$, Fig. 2, right).

In the correlation analysis, the dosage of antipsychotics and the PANSS total and subscale scores did not show any significant correlation with the LDAEP values. When age, sex, and smoking were controlled, there was a significant correlation of the LDAEP values with illness duration ($r = -0.259$, $p = 0.045$, Fig. 3).

4. Discussion

In this study, we evaluated the LDAEP pattern for 64 schizophrenia patients with a wide range of illness duration, and 50 healthy controls. Patients with schizophrenia showed different strengths of the LDAEP according to the chronicity of pathology. Furthermore, the LDAEP values were negatively correlated with illness duration in patients with schizophrenia.

Previous studies using techniques like cerebrospinal fluid tapping, genetics, and neuroimaging and drug responsiveness have reported increased 5-HT neurotransmission in patients with schizophrenia (Meltzer, 1999; Sawa and Snyder, 2002). In addition, lower LDAEP values (supposed higher central 5-HT neurotransmission) were found in patients with schizophrenia compared with normal controls (Juckel

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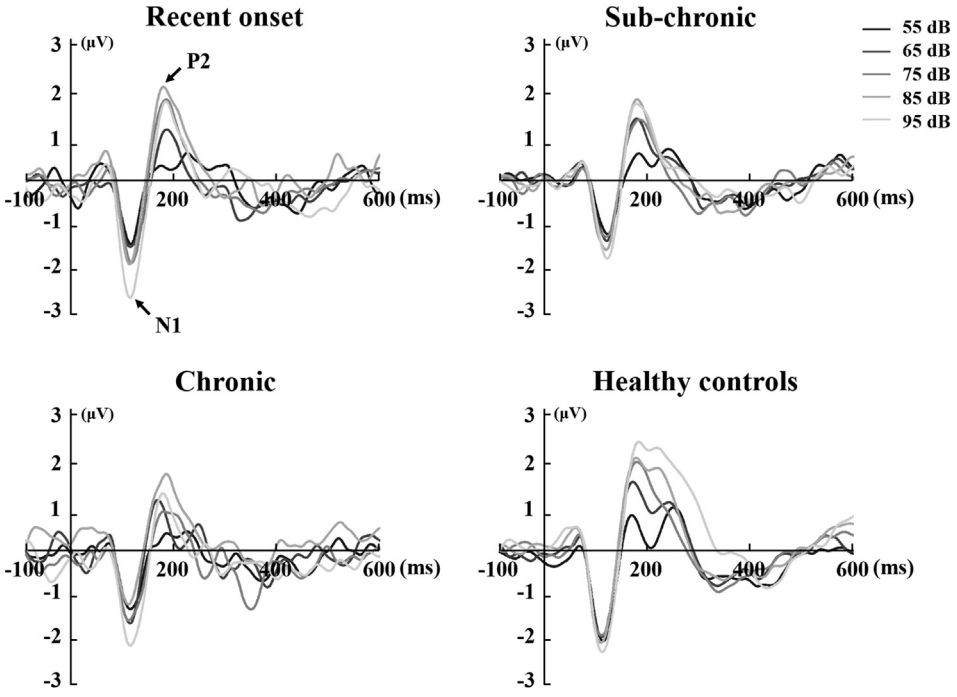

Fig. 1. ERP waveforms for each group with separate waves for each loudness level.

et al., 2003). The hypothesis of increased central 5-HT neurotransmission in schizophrenia using the LDAEP had been replicated (Juckel et al., 2008; Park et al., 2010). Serotonin neurotransmission is proposed to be a trait marker for schizophrenia as similar elevations in neurotransmission have been found during prodromal, acute, and chronic phases (Gudlowski et al., 2009). However, in the current study, the LDAEP differed significantly across groups with differing durations of schizophrenia, such as recent onset, sub-chronic, and chronic schizophrenia. In addition, the reduction in LDAEP was proportional to the duration of illness. Our results are in line with previous studies, most studying patients of chronic stages of the illness, with respect to higher levels of central 5-HT neurotransmission in patients with schizophrenia. However, our results showed that the LDAEP changed according to the chronicity of illness. The LDAEP was lower in the chronic group than in the recent onset group, although the dosage of antipsychotics increased as the duration of illness increased. This means that the LDAEP could be a state marker, rather than a trait marker, in patients with schizophrenia.

It is noteworthy that despite higher doses of antipsychotics (5-HT-dopamine antagonists) in chronic groups compared to the recent onset group, 5-HT neurotransmission in the chronic group was stronger compared to recent onset group. These findings suggest that dosage of medication may not have any significant effect on the LDAEP value. Previous studies have shown that antipsychotic medication did not significantly change central serotonergic turnover. In a study of 5-HT1A receptor density, individuals treated with clozapine (moderate 5-HT1A receptor activity) showed no differences when compared with either healthy controls or participants treated with antipsychotic medications without 5-HT1A receptor activity (Bantick et al., 2004). Andreou et al. (2014) evaluated a major monoamine metabolite in the cerebrospinal fluid (CSF) of patients with psychotic disorders; they found that CSF 5-hydroxyindoleacetic acid (5-HIAA, 5-HT metabolite) concentrations were not associated with antipsychotic treatment. Scheepers et al. (2001) evaluated CSF monoamine metabolite concentrations before and after olanzapine treatment in patients with schizophrenia. They reported that olanzapine treatment increased levels of homovanillic acid (HVA, a dopamine metabolite) and the HVA/5-HIAA ratio in CSF from patients with schizophrenia, but not 5-HIAA concentrations. These previous results support the null or minimal effect of second generation antipsychotics on central serotonergic function.

Regarding negative symptoms of schizophrenia, decreased 5-HT neurotransmission in patients with predominant negative symptoms was found (Wyss et al., 2013). By contrast, in another study, patients with predominant negative symptoms showed increased 5-HT neurotransmission (Juckel, 2015). Anand et al. (2002) evaluated levels of CSF amines and their metabolites in first episode drug-naive schizophrenia patients. They reported a significant negative correlation between CSF 5-HIAA levels and negative and disorganized symptoms,

Table 1
Comparison of demographic and clinical variables among patients with recent onset, sub-chronic, and chronic schizophrenia and healthy controls.

Variable	Recent onset group (n = 21)	Sub-chronic group (n = 28)	Chronic group (n = 15)	Healthy controls (n = 50)	*p*
Age, years	30.52 ± 9.48	33.46 ± 11.49	39.33 ± 9.70	33.06 ± 11.04	0.10
Sex (M/F)	8/13	14/14	8/7	25/25	0.77
Education, years	12.90 ± 2.84	13.40 ± 2.91	13.71 ± 2.99	13.94 ± 4.10	0.78
Smoking (no/yes)	2/19	5/23	5/10	7/44	0.12
Antipsychotics[a]	500.79 ± 383.37	469.00 ± 277.25	903.93 ± 1057.53		0.07[b]
PANSS, total	82.38 ± 23.40	83.36 ± 19.78	87.73 ± 12.15		0.70[b]
PANSS, positive	20.29 ± 8.42	20.36 ± 6.28	23.87 ± 4.89		0.21[b]
PANSS, negative	20.81 ± 6.62	21.39 ± 6.80	22.13 ± 8.22		0.85[b]
PANSS, general	41.29 ± 12.35	43.75 ± 8.60	41.73 ± 10.51		0.68[b]

[a] Chlorpromazine equivalents.
[b] Three group ANOVA.

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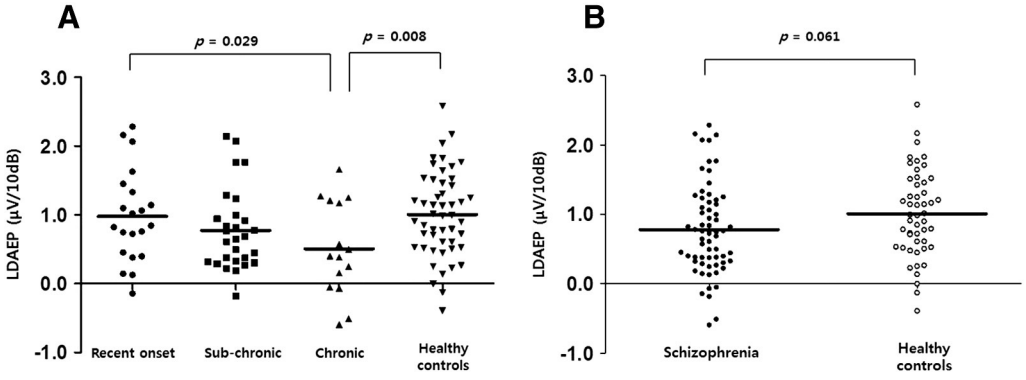

Fig. 2. (A) Comparison of the LDAEP among patients with recent onset, sub-chronic and chronic schizophrenia, and healthy controls. Standard error bars are presented. (B) Comparison of the LDAEP between patients with schizophrenia and healthy controls.

and between CSF HVA levels and psychosis symptoms. The current results do not correspond with these previous studies and more studies with larger cohorts are needed in the future.

There are several limitations to the current study. First, the relatively small sample size limits the generalization of our findings. Second, the LDAEP was not measured in a drug-free state. However, controlling dosage of antipsychotics as a covariate demonstrated that this factor did not significantly affect the results. Considering these limitations, further investigations involving a drug-free state and larger sample sizes are warranted to fully understand the 5-HT-related pathophysiology of schizophrenia using LDAEP.

In conclusion, the present study demonstrates that the LDAEP changes according to the duration of illness in patients with schizophrenia. This means that the LDAEP could be a state marker, rather than a trait marker, in patients with schizophrenia.

Role of the funding source

This work was supported by a grant from the Korea Science and Engineering Foundation (KOSEF) funded by the Korean government (MOST; No. M10644000005-06 N4400-00510), The KOSEF had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Young-Min Park and Seung-Hwan Lee designed the study. Young-Min Park wrote the manuscript. Seung-Hwan Lee wrote the protocol. Eunjoo Jung, Hyang Sook Kim, and Sang Woo Hahn helped with data collection and consulted on data processing. Seung-Hwan Lee supervised the study and writing of the manuscript. All authors have contributed to and have approved the final manuscript.

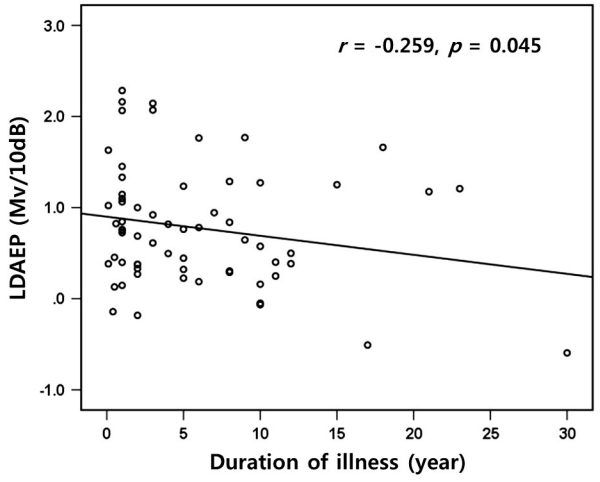

Fig. 3. Scattergram of Pearson partial correlation between LDAEP and duration of illness in patients with schizophrenia.

Conflict of interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors thank Sun Hae Jeon and Jeong-In Kim for their assistance with data collection.

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Please cite this article as: Park, Y.-M., et al., Differences in central serotoninergic transmission among patients with recent onset, sub-chronic, and chronic schizophrenia as ass..., Schizophr. Res. (2015), http://dx.doi.org/10.1016/j.schres.2015.07.036