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Letter to the Editor

Gamma-band auditory steady-state response is associated with plasma levels of D-serine in schizophrenia: An exploratory study

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Dear Editors,

The gamma-band auditory steady-state response (ASSR) is reduced in schizophrenia and is considered a candidate biomarker for schizophrenia (Koshiyama et al., 2018; Light et al., 2006; Tada et al., 2016; Thuné et al., 2016). While the gamma-band ASSR is considered to reflect γ-aminobutyric acid (GABA)-ergic interneuron function (Gonzalez-Burgos et al., 2015), recent animal studies have shown that *N*-methyl-D-aspartate (NMDA) receptor dysfunction in parvalbumin-positive GABAergic interneurons causes deficits in gamma oscillations (Carlen et al., 2012; Nakao and Nakazawa, 2014). Because NMDA receptor function is thought to be altered in schizophrenia (Brouwer et al., 2013; Bustillo et al., 2014), these results suggest that NMDA receptor dysfunction may be associated with a reduction in the gamma-band ASSR in patients with schizophrenia. Furthermore, it is known that plasma levels of glutamatergic amino acids, which are the co-agonists of the NMDA receptor and are considered to be biological indices that reflect NMDA receptor function, are significantly correlated with the cerebrospinal fluid levels of glutamatergic amino acids in human subjects (D'Souza et al., 2000). In the current study, we investigated the relationship between the gamma-band ASSR, which was significantly impaired in patients with schizophrenia compared with healthy controls, and plasma levels of glutamatergic amino acids in the schizophrenia and healthy control groups to further develop the gamma-band ASSR as a biological indicator not only for GABAergic interneuron function but also for NMDA receptor function in schizophrenia.

Twenty-three individuals with schizophrenia and 22 healthy controls participated in this study (Table S1). Written informed consent was obtained from each subject before participation. The Research Ethics Committee of the Faculty of Medicine, University of Tokyo, approved this study (approval No. 629, 2094, 2226). We performed the ASSR paradigm and calculated the intertrial phase coherence (ITC) and the event-related spectral perturbation (ERSP) as the ASSR indices, as has been previously described (Tada et al., 2016; topographies are shown in Fig. S1). We calculated the mean ITC and ERSP at FCz by averaging the data over the first 500 ms within a trial (0–500 ms) for the frequency range (40 Hz: 36–45 Hz). We also calculated the mean ITC and ERSP for each 100-ms epoch for time-course analyses for supplementary information. Since we obtained electroencephalographic data with two types of electrodes, we converted the raw ASSR measures to z-scores and employed the z-scores for the following statistical analyses. Plasma levels of the peripheral glutamatergic amino acids glutamate, glutamine, glycine, D-serine, and L-serine were measured, and the relative D-serine level [100 × (D-serine)/(D-serine + L-serine)] (%) was calculated. Details of the methods are described in the Supplementary Methods.

The time-course and grand average time-frequency maps for ITC and ERSP at FCz for each group are shown in Fig. 1 and Fig. S2. There was a significant difference between the groups in the ERSP (0–500 ms; $t_{43} = -1.87$, $p = 0.03$) but not in the ITC (0–500 ms; $t_{43} = -0.48$, $p = 0.32$). In addition, there was a significant difference between the groups in the ITC (0–100 ms; Table S2). As previous studies have already shown reduced ASSR in schizophrenia, a p-value of <0.05 (one-tailed) was considered statistically significant (Thuné et al., 2016). The plasma levels of glutamatergic amino acids [D-serine ($t_{43} = -0.22$, $p = 0.83$), L-serine ($t_{43} = -1.26$, $p = 0.22$), relative D-serine ($t_{43} = 0.80$, $p = 0.43$; Fig. S3), glutamine ($t_{43} = 0.71$, $p = 0.48$), glycine ($t_{43} = -1.17$, $p = 0.25$), or glutamate ($t_{43} = 1.29$, $p = 0.20$)] did not differ between patients and healthy controls [the significance level was set at $p < 0.05$ (two-tailed); Table S3].

The ERSP (0–500 ms) had a significant correlation with the plasma levels of relative D-serine in patients ($r = 0.67$, $p = 0.001$; Fig. 1) but not in healthy controls ($r = 0.21$, $p = 0.36$; Table S4). The ITC (0–500 ms) did not have significant correlations with the plasma levels of relative D-serine in patients ($r = 0.34$, $p = 0.12$) or in healthy controls ($r = 0.19$, $p = 0.41$). The plasma levels of all other amino acids were not significantly correlated with the ERSP (0–500 ms) or the ITC (0–500 ms) in patients or healthy controls. Here, we applied the Bonferroni correction with two indices of the ASSR, six amino acids and two groups, and a p-value of <0.05/24 = 0.002 was considered statistically significant. Additionally, the plasma levels of relative D-serine was significantly correlated with the ERSP (100–200 ms, 200–300 ms, 300–400 ms, and 400–500 ms) and the ITC (100–200 ms, 200–300 ms, 300–400 ms, and 400–500 ms) in patients (the statistical significance level was set at uncorrected $p < 0.05$; Table S4). Antipsychotic dose was not significantly correlated with ERSP (0–500 ms; $r = -0.07$, $p = 0.77$) or plasma levels of relative D-serine ($r = -0.13$, $p = 0.55$) in patients. Although the time interval between the blood draw and the electroencephalography was significantly different between the groups ($t_{43} = 2.62$, $p = 0.01$), the partial correlation analyses adjusted to the time interval also showed a significant correlation between the ERSP and the plasma levels of relative D-serine in schizophrenia ($r = 0.66$, $p = 0.001$; Table S5).

This is the first study to report the relationship between the gamma-band ASSR and the plasma levels of D-serine in schizophrenia. Our results indicate that the gamma-band ASSR may reflect NMDA receptor function. Because no correlation between the gamma-band ASSR and plasma levels of relative D-serine was observed in healthy controls, the correlation observed in the patients with schizophrenia may reflect a pathological process associated with the NMDA receptor in schizophrenia. These findings suggest that the gamma-band ASSR may reflect not

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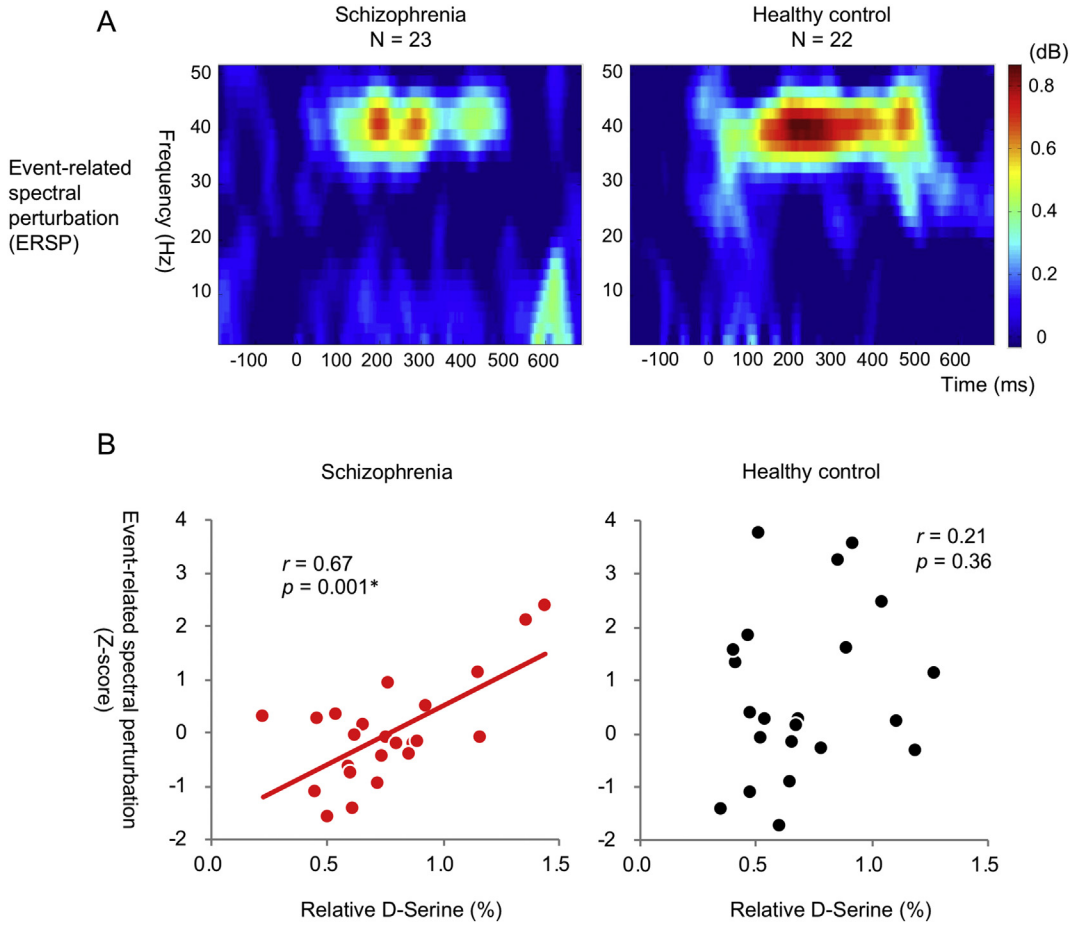

Fig. 1. The grand average time-frequency maps for event-related spectral perturbation (ERSP) at FCz (A) and correlations between the ERSP and the plasma levels of relative D-serine in patients with schizophrenia or in healthy controls (B). Legends: The x-axis indicates time (ms), the y-axis indicates frequency (Hz), and the color scale indicates the ERSP at each time-frequency point (A). The x-axis indicates the plasma levels of relative D-serine, and the y-axis indicates ERSP (z-score); the asterisk indicates a corrected $p < 0.05$ (B).

only GABAergic interneuron function but also NMDA receptor function in patients with schizophrenia (details of the discussion are described in the Supplementary Discussion).

Conflict of interest

The authors declare no conflict of interest.

Contributors

D. Koshiyama, K. Kirihara, M. Tada, T. Nagai, M. Fujioka, S. Koike and M. Suga collected the data. D. Koshiyama, K. Kirihara, M. Tada, T. Nagai and K. Usui analyzed the data. D. Koshiyama, K. Kirihara, M. Tada, T. Nagai, M. Fujioka, K. Usui, S. Koike, M. Suga and T. Araki interpreted the results. D. Koshiyama, K. Kirihara, M. Tada, T. Nagai and T. Araki designed the study. K. Hashimoto and K. Kasai supervised all aspects of collection, analysis, interpretation and design of the data. D. Koshiyama, K. Kirihara, and K. Kasai wrote the manuscripts. All authors contributed to and have approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.02.012.

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