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Auditory gamma oscillations predict global symptomatic outcome in the early stages of psychosis: A longitudinal investigation

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HIGHLIGHTS

- 40-Hz auditory steady-state response (ASSR) predicts the prognosis in early psychosis in this study.
- 40-Hz ASSR reduction correlates with global symptomatic outcome after 1–2 years.
- 40-Hz ASSR may be a useful biomarker of the long-term prognosis in early psychosis.

ABSTRACT

Objectives: The gamma-band auditory steady-state response (ASSR) is thought to reflect the function of parvalbumin-positive γ-aminobutyric acid (GABA)-ergic interneurons and may be a candidate biomarker in early psychosis. Although previous cross-sectional studies have shown that gamma-band ASSR is reduced in early psychosis, whether reduced gamma-band ASSR could be a predictor of the long-term prognosis remains unknown.
Methods: In this longitudinal study, we investigated the association between gamma-band ASSR reduction and future global symptomatic or functional outcome in early psychosis. We measured 40-Hz ASSR in 34 patients with recent-onset schizophrenia (ROSZ), 28 ultra-high risk (UHR) individuals, and 30 healthy controls (HCs) at baseline. After 1–2 years, we evaluated the global assessment of functioning (GAF) in the ROSZ (N = 20) and UHR (N = 20) groups.
Results: The 40-Hz ASSR was significantly reduced in the ROSZ and UHR groups. The attenuated 40-Hz ASSR was correlated with the future global symptomatic outcome in the ROSZ, but not in the UHR groups.
Conclusions: A reduction in the gamma-band ASSR after the onset of psychosis may predict symptomatic outcomes in early psychosis.
Significance: Gamma-band ASSR may be a potentially useful biomarker of the long-term prognosis in patients with recent-onset schizophrenia.

1. Introduction

The gamma-band auditory steady-state response (ASSR) is hypothesized to be a useful biomarker for psychosis (Uhlhaas and Singer, 2010). Kwon et al. (1999) performed the first study of 40-Hz ASSR in patients with schizophrenia using electroen-

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cephalography (EEG) and demonstrated a reduced power and synchronization in response to 40-Hz stimulation, but not to the 20-Hz stimulation, in these patients. This initial finding has been replicated in many studies using EEG (Brenner et al., 2003; Hamm et al., 2015; Hirano et al., 2015; Kirihara et al., 2012; Light et al., 2006; Spencer et al., 2008; Tada et al., 2016) or magnetoencephalography (MEG; Edgar et al., 2014; Teale et al., 2008; Tsuchimoto et al., 2011; Vierling-Claassen et al., 2008; Wilson et al., 2008). A recent meta-analysis confirmed that the 40-Hz ASSR is impaired in patients with schizophrenia (Thune et al., 2016).

Synaptic interactions between parvalbumin-positive γ-aminobutyric acid (GABA)-ergic interneurons and pyramidal neurons evoke cortical gamma oscillations (Cardin et al., 2009; Sohal et al., 2009). Abnormalities in parvalbumin-positive GABAergic interneurons, such as reduced expression of the GABA-synthesizing enzyme glutamic acid decarboxylase 67 (GAD67; Akbarian and Huang, 2006) and parvalbumin (Eyles et al., 2002) in cortical neurons, have been observed in the postmortem brains of individuals with schizophrenia. Thus, investigating gamma oscillations may be meaningful for the understanding of GABAergic interneuron dysfunction in schizophrenia (Fisahn et al., 2009; Gonzalez-Burgos et al., 2015).

Recent studies have focused on early stages of psychosis because early detection and intervention may improve the functional outcome of persons with psychotic disorders (Farooq et al., 2009; Marshall et al., 2005; Perkins et al., 2005). Several clinical criteria have been developed to identify people who have an ultra-high risk (UHR) for developing psychosis (Cannon et al., 2008; Ruhrmann et al., 2010). The gamma-band ASSR is impaired in patients with first episode psychosis (Spencer et al., 2008; Tada et al., 2016). For UHR subjects, Tada et al. (2016) demonstrated time-course specific alteration of ASSR, with a reduction in the late-latency component and an intact early-latency component. These findings suggest that gamma-band ASSR may have clinical utility in the early stages of psychosis. Gamma-band ASSR is thought to reflect the activity of GABAergic interneurons, hence gamma-band ASSR may serve as a potential biomarker that links biological mechanisms such as the function of GABAergic interneurons to clinical utility such as development of intervention improving prognosis in the early stages of psychosis.

Several previous cross-sectional studies have reported correlations between 40-Hz ASSR and cognitive function in the early stages of psychosis. Light et al. (2006) reported a positive correlation between the 40-Hz ASSR and the working memory performance in patients with schizophrenia. Furthermore, Tada et al. (2016) demonstrated a positive correlation between the 40-Hz ASSR and attentional functioning in first episode schizophrenia. These findings suggest that a reduction of the 40-Hz ASSR may reflect the neurobiological mechanisms underlying cognitive impairments in schizophrenia. Because cognitive function is an important predictor of functional outcome in first-episode schizophrenia (Milev et al., 2005), the gamma-band ASSR may predict prognosis in the early stages of psychosis. However, to the best of the authors' knowledge, there is no longitudinal study investigating whether the gamma-band ASSR could predict prognosis in the early stages of psychosis.

In this longitudinal study, we measured the gamma-band ASSR, global symptomatic/functional outcome at baseline, and global symptomatic/functional outcome after 1–2 years from baseline in the early stages of psychosis. We tested whether the gamma-band ASSR at baseline was associated with (i) global symptomatic/functional outcome at baseline and (ii) future global symptomatic/functional outcome in the early stages of psychosis. Additionally, we tested whether the gamma-band ASSR at baseline was associated with (iii) average scores of global symptomatic/functional outcome at baseline and follow-up evaluations and (iv) a change in global symptomatic/functional scores between baseline and follow-up evaluation as the secondary analysis for supplementary information.

2. Methods

2.1. Subjects

We recruited 34 patients with recent-onset schizophrenia (ROSZ), 28 individuals with UHR, and 30 healthy controls (HCs) at baseline (Time 1). At baseline, we recorded EEGs from the ROSZ group, the UHR group, and the HCs, and assessed the global symptomatic/functional outcome of the ROSZ and UHR groups. One to 2 years from baseline (Time 2), we assessed the global symptomatic/functional outcome of the participants from the ROSZ (N = 20) and UHR (N = 20) groups. Fourteen of 34 patients with ROSZ, and 8 of 28 individuals with UHR were lost to follow-up at Time 2. The ASSRs from a subset of these participants (N = 9 ROSZ participants and N = 11 UHR participants) were previously published as a cross-sectional study (Tada et al., 2016). The ROSZ and UHR participants were recruited from outpatient and inpatient units at the University of Tokyo Hospital. Most participants were registered at the outpatient unit specialized for early intervention. HCs were recruited through advertisements at several universities in Tokyo.

Inclusion criteria at baseline for the ROSZ group were: (i) participants aged 15–40 years, (ii) participants who had received a diagnosis of schizophrenia using the diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV) by an experienced clinical psychiatrist (D.K., M.T., T.N., K.M., K.S., J.M., or Y.S.), and the diagnosis was reviewed by a clinical review board, and iii) participants who had experienced the first psychotic symptoms within the past 60 months. Of the total ROSZ sample (N = 20), 15 patients participated in the integrative neuroimaging studies in schizophrenia targeting for early intervention and prevention (IN-STEP) project (Koike et al., 2013). Twelve of the 15 participants underwent EEG measurement at the first assessment point for the IN-STEP project. All 12 participants satisfied the criteria of first-episode schizophrenia (FES): emergence of the first psychotic symptoms within the past 60 months and no history of antipsychotic drug treatment for more than 16 cumulative weeks at entry into the IN-STEP project. The initial EEG testing of the other 3 participants was performed during the follow-up period of IN-STEP (Time 1). Clinical assessments of the 3 participants were performed at Time 1 and at the next assessment point for the IN-STEP project (Time 2). The 3 participants did not satisfy the criteria of FES but satisfied the criteria of ROSZ. We included another 5 patients with ROSZ who had participated in the other project and whose EEG data at Time 1 (baseline) and clinical data at Time 1 and Time 2 (1 to 2 years from baseline) were available. Inclusion criteria at baseline for the UHR group were: (i) participants aged 15–30 years and (ii) participants identified as UHR using the structured interview for prodromal symptoms (SIPS; Kobayashi et al., 2007). Inclusion criteria of HCs were: (i) participants aged 15–40 years and (ii) participants with no personal history of psychiatric disease or a family history of axis I disorders in first-degree relatives. Exclusion criteria for all groups are listed as follows: neurological illness, traumatic brain injury with loss of consciousness for more than five minutes, history of electroconvulsive therapy, low premorbid intelligence quotient (IQ below 70), previous alcohol/substance abuse or addiction, and hearing impairment assessed with a hearing test in both ears at 30-dB at 1000 Hz and 40-dB at 4000 Hz by audiometer. Written informed consent was obtained from each subject before participation. The current study was approved by the Research Ethics Committee of the Faculty of Medicine, The