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Progressive reduction of auditory evoked gamma in first episode schizophrenia but not clinical high risk individuals

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ABSTRACT

The early auditory-evoked gamma band response (EAGBR) may serve as an index of the integrity of fast recurrent inhibition or synaptic connectivity in the auditory cortex, where abnormalities in individuals with schizophrenia have been consistently found. The EAGBR has been rarely investigated in first episode schizophrenia patients (FESZ) and individuals at clinical high risk (CHR) for schizophrenia, and never been compared directly between these populations nor evaluated longitudinally. Here we examined the EAGBR in FESZ, CHR, and matched healthy controls (HC) at baseline and 1-year follow-up assessments to determine whether the EAGBR was affected in these clinical groups, and whether any EAGBR abnormalities changed over time. The electroencephalogram was recorded with a dense electrode array while subjects (18 FESZ, 18 CHR, and 40 HC) performed an auditory oddball task. Event-related spectral measures (phase locking factor [PLF] and evoked power) were computed on Morlet-wavelet-transformed single epochs from the standard trials. At baseline, EAGBR PLF and evoked power did not differ between groups. FESZ showed progressive reductions of PLF and evoked power from baseline to follow-up, and deficits in PLF at follow-up compared to HC. EAGBR peak frequency also increased at temporal sites in FESZ from baseline to follow-up. Longitudinal effects on the EAGBR were not found in CHR or HC, nor did these groups differ at follow-up. In conclusion, we detected neurophysiological changes of auditory cortex function in FESZ during a one-year period, which were not observed in CHR. These findings are discussed within the context of neurodevelopmental models of schizophrenia.

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1. Introduction

Abnormalities in the auditory cortex have been one of the most consistent findings in studies of patients with schizophrenia (Javitt and Sweet, 2015). Neuropathological studies have found abnormalities in elements of cortical microcircuits (e.g., Chance et al., 2008; Sweet et al., 2009). The volumes of regions of the auditory cortex are reduced already in the early course of the illness (Hirayasu et al., 2000) and show progressive reduction longitudinally (Kasai et al., 2003). The lateralization of auditory cortex volume is also abnormal (Chance et al., 2008; Kasai et al., 2003). Auditory event-related potentials (ERPs) are impaired in schizophrenia (Rosburg et al., 2008), with these deficits being correlated with auditory cortex volume reduction (McCarley et al., 1993; Salisbury et al., 2007). And, functional neuroimaging studies have reported abnormal auditory cortex activity (Ford et al., 2009; Hoffman et al., 2007; Lennox et al., 2000; Mayer et al., 2013). These structural and functional abnormalities are often related to auditory hallucination symptoms (Ford et al., 2009; Hoffman et al., 2007; Lennox et al., 2000; Spencer et al., 2008).

Oscillatory neuronal activity in the γ band (30–100 Hz) of the electroencephalogram (EEG) is involved in the representation and selection of information and has been implicated in a number of perceptual, cognitive, and motor functions (Bosman et al., 2014). The generation of γ

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oscillations relies upon inhibition from fast-spiking interneurons that express the calcium-binding protein parvalbumin (PV) (Bartos et al., 2007; Sohal et al., 2009; Whittington and Traub, 2003), as well as upon a minimal amount of synaptic connectivity between neurons (Börgers et al., 2012; Spencer, 2009). Thus, γ oscillations may index the integrity of recurrent inhibition from PV interneurons to pyramidal cells, as well as synaptic connectivity in cortical microcircuits. There is substantial evidence for both abnormalities of γ-amino-butyric acid (GABA) neurotransmission in schizophrenia, including reduced synthesis of GABA in PV interneurons (Gonzalez-Burgos and Lewis, 2008; Lewis and Gonzalez-Burgos, 2008), and for reduced synaptic connectivity in the cortex (Hayashi-Takagi and Sawa, 2010). In the auditory cortex of schizophrenia patients, reduced expression of the GABA-synthesizing enzyme GAD65 (Moyer et al., 2012) and reduced synaptic connectivity (Sweet et al., 2009) have been found as well. Therefore, auditory-evoked γ oscillations might be used to index the integrity of fast recurrent inhibition or synaptic connectivity in the auditory cortex in schizophrenia. In fact, deficits of the auditory steady-state response (ASSR) (Brenner et al., 2009; Thuné et al., 2016) and early auditory-evoked γ band response (EAGBR) (Hall et al., 2011; Leicht et al., 2010; Lenz et al., 2011; Roach and Mathalon, 2008) have been observed in schizophrenia patients compared to healthy individuals.

In order to understand the risk factors and development of schizophrenia, it is important to investigate not only chronic patients but also patients hospitalized for their first psychotic episode (FESZ) and individuals at imminent clinical high risk (CHR) for developing schizophrenia. To our knowledge there have been only one published study of the EAGBR in CHR and two studies of the EAGBR in FESZ. In CHR, Perez et al. (2013) found that EAGBR evoked power was reduced but EAGBR phase locking factor (PLF) did not differ compared with healthy individuals. In FESZ, Leicht et al. (2015) and Taylor et al. (2013) reported reduced EAGBR evoked power and PLF. The generalizability of these findings has yet to be determined, the EAGBR in CHR and FESZ have yet to be directly compared, and the progression of EAGBR deficits over time has not been examined. Therefore, in the present study we examined the EAGBR in matched groups of CHR, FESZ, and healthy control subjects (HC) at a baseline assessment and a 1-year follow-up to determine whether: 1) EAGBR deficits were present in CHR and FESZ compared to HC and to each other, and 2) any such deficits change over time.

2. Methods

2.1. Participants

The final sample consisted of 18 CHR, 18 FESZ, and 40 HC. Participants were recruited through the Boston CIDAR Center (https://bricweb.bidmc.harvard.edu/bostoncidar). CHR and FESZ were recruited by referrals from clinicians or through local hospitals and clinics, and HC were recruited through newspaper and website advertisements. The study was approved by the IRBs of Harvard Medical School, Beth Israel Deaconess Medical Center, Cambridge Hospital, Brigham and Women's Hospital, Massachusetts General Hospital, and the Veteran Affairs Boston Healthcare System. All participants (or legal guardians for those under 18) gave written informed consent prior to study participation, and received payment for participation.

Exclusion criteria for all participants were: sensory-motor handicaps; neurological disorders; medical illnesses that significantly impair neurocognitive function; diagnosis of mental retardation; education <5th grade if under 18 years of age, or <9th grade if 18 years or above; not fluent in English; DSM-IV substance abuse in the past month; DSM-IV substance dependence, excluding nicotine, in the past 3 months; current suicidality; history of electroconvulsive therapy within the past five years for CHR and FESZ and history of electroconvulsive therapy ever for HC; and study participation by another family member. Additionally, participants who had <6 months inter-measurement interval and excess artifacts after artifact removal were excluded from further analysis (see Supplemental Text). Substance use was assessed with the substance use disorders modules of the Structured Clinical Interview for DSM-IV-TR (SCID; First et al., 2002) and questionnaires developed by our group. We examined the temporal relationship between substance use and prodromal symptoms to determine if the substance use appeared causative. All participants were also assessed with the Diagnostic Interview of Personality Disorders (Zanarini et al., 1987).

FESZ met DSM-IV-TR criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder. DSM-IV diagnoses were based on interviews using the SCID and information from medical records. First episode was operationally defined as the first psychiatric hospitalization. Mean duration of illness in FESZ at baseline was 15.6 ± 16.2 months.

CHR inclusion criteria were assessed with the Scale of Prodromal Symptoms (SOPS; Miller et al., 1999). Exclusion criteria for CHR were DSM-IV diagnosis of a psychotic disorder, and the presence of substance-induced or other medically-induced prodromal symptoms. All but two participants met criteria for Attenuated Positive Symptoms Syndrome, the remaining two meeting criteria for Genetic Risk and Deterioration Syndrome. There was one CHR participant who subsequently converted to schizophrenia in our sample, who was excluded from further analyses in order to reduce heterogeneity. The statistical results reported below remained basically the same when analyzed with the converter (see Fig. 3).

HC were drawn from the same geographic bases as the CHR and FESZ, with comparable age, gender, race and ethnicity, handedness (Annett, 1970), and parental socioeconomic status (Hollingshead, 1965). No HC met criteria for any current major DSM-IV-TR Axis I disorders, or a history of psychosis, major depression (recurrent), bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, or developmental disorders. HC were also excluded for a history of psychiatric hospitalizations, prodromal symptoms, schizotypal or other Cluster A personality disorders, first degree relatives with psychosis, or any current or past use of antipsychotics. Other past psychotropic medication use was acceptable, but the subjects must have been off medicine for at least 6 months before participating in the study, except for pro re nata medications like sleeping medications or anxiolytic agents (such as beta-blockers for performance anxiety, tremors, etc.).

Premorbid intellectual abilities were estimated using the Reading subtest from the Wide Range Achievement Test-4 (Wilkinson and Robertson, 2006) and current intellect was estimated from the Vocabulary and Block Design subtests of the Wechsler abbreviated Scale of Intelligence (Wechsler, 1999). All participants were evaluated with the Global Assessment of Functioning scale (DSM-IV-TR). In addition, CHR symptoms were assessed with the SOPS. FESZ symptoms were rated using the Scale for the Assessment of Positive Symptoms (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (Andreasen, 1983).

2.2. Stimuli and task

Participants performed a standard auditory oddball task. For details please see the Supplemental Text.

2.3. EEG acquisition and processing

The EEG was recorded from a dense electrode array, and artifacts were removed with independent component analysis. The EAGBR was measured with evoked power and PLF computed with the Morlet wavelet transform. The N1 and P2 ERP component amplitudes were also measured. For details please see the Supplemental Text.

2.4. Statistical analyses

Group differences in demographic variables were analyzed using one-way ANOVA, chi-square, and *t*-tests. EAGBR PLF and evoked power were measured at fronto-central (F1/Fz/F2, FC1/FCz/FC2, C1/Cz/C2) and temporal (M1/M2, CP5/CP6, TP7/TP8, P5/P6, P7/P8, P9/P10, PO7/PO8) sets of electrodes at which the EAGBR was maximal (see Fig. 2). EAGBR measures were evaluated in cross-sectional and longitudinal analyses using mixed-model ANOVAs with the factor Group (HC, CHR, FESZ). Electrode factors were Midline (frontal, fronto-central, central) and Lateral (left, midline, right) for the fronto-central component of the EAGBR, and Electrode Pair (see above) and Hemisphere (left, right) for the temporal component. Longitudinal analyses included the factor Time (baseline, follow-up). The degrees of freedom were adjusted with the Huynh-Feldt epsilon for factors with >2 levels. Tukey's honestly significant difference test was used for post hoc comparisons. Effect sizes were calculated with Cohen's d. Spearman's ρ (2-tailed) was used for correlations. For all statistical tests $\alpha = 0.05$. For the selection of time-frequency windows, please see the Supplemental Text.

3. Results

3.1. Demographic, clinical, and task performance variables

Please see details in the Supplemental Text and Table 1.

3.2. EAGBR cross-sectional analyses

The grand average time-frequency maps of PLF and evoked power are shown in Fig. 1 for the baseline and follow-up assessments. Topographic maps of PLF and evoked power are shown in Fig. 2. Scatterplots of EAGBR changes from baseline to follow-up are presented in Fig. 3.

3.2.1. PLF

At baseline, for both the fronto-central and temporal components of the EAGBR, there was no significant effect of Group or interaction with Group on PLF or PLF peak frequency (F's < 1.81, p's > 0.17, and −0.56 < d's < 0.31).

At follow-up, the main effect of Group on PLF was significant for the temporal component ($F[2,73] = 3.26$, $p = .04$), which reflected the EAGBR reduction in FESZ compared with HC ($p = .03$, $d = 0.86$). There were no significant differences between HC and CHR ($p = .76$,$d = 0.18$), nor CHR and FESZ ($p = .26$, $d = 0.53$). For the fronto-central component, the main effect of Group was only marginally significant ($F[2,73] = 2.90$, $p = .06$).

For PLF peak frequency, the main effect of Group was significant at temporal sites at follow-up ($F[2,73] = 5.0$, $p = .009$), due to the increased EAGBR frequency in FESZ (48.2±4.3 Hz) compared with HC (44.8±3.8 Hz) ($p = .011$). PLF peak frequency did not differ among groups at fronto-central sites.

3.2.2. Evoked power

For the fronto-central and temporal EAGBR components there were no significant main effects of Group or interaction with Group at either assessment time (F's < 2.27, p's > 0.11, −0.49 < d's < 0.65). Likewise, there were no significant effects on evoked power peak frequency.

3.3. EAGBR longitudinal analyses

3.3.1. PLF

In both the fronto-central and temporal components of the EAGBR there were significant main effects of Time (fronto-central: F[1,73] =

Table 1
Demographic, neurocognitive, and clinical information.

	HC	CHR	FESZ	Statistic	*p*
# Male/female	24/16	9/9	14/4	$X^2(2) = 3.1$	0.22
Age at baseline (year)	21.5 ± 3.6	21.2 ± 3.9	23.1 ± 4.1	$F(2,73) = 1.39$	0.25
EEG interval (month)	12.2 ± 3.4	11.5 ± 1.8	12.2 ± 4.4	$F(2,73) = 0.33$	0.72
Handedness[a]	1.4 ± 3.3	0.9 ± 2.9	2.5 ± 4	$F(2,73) = 1.11$	0.34
Premorbid IQ[b]	113.4 ± 15.3	112.3 ± 19.7	112.8 ± 13.2	$F(2,73) = 0.03$	0.97
Current IQ[c]	115.8 ± 21.9	116.1 ± 11.7	111.1 ± 12.2	$F(2,73) = 0.49$	0.61
Education years	14 ± 2.7	13.1 ± 2.3	14.0 ± 2.5	$F(2,73) = 0.78$	0.46
PSES	1.8 ± 0.9	2.1 ± 0.9	2.3 ± 1.0	$F(2,73) = 2.13$	0.13
GAF at baseline	84.2 ± 8.3	50.6 ± 9.6	51.0 ± 9.3	$F(2,73) = 134.5$	<0.001*
GAF at followup	82.7 ± 9.4	57.7 ± 8.2	61.5 ± 15.4	$F(2,69) = 40.88$	<0.001*
Target count Accuracy at baseline (%)	94.5 ± 12.1	97.5 ± 4.0	91.4 ± 28.5	$F(2,73) = 0.64$	0.53
Target count Accuracy at follow-up (%)	98.0 ± 3.3	98.6 ± 2.0	94.6 ± 10.9	$F(2,73) = 2.63$	0.08
SOPS positive score at baseline		11.4 ± 4.3			
SOPS positive score at follow-up		8.9 ± 5.0			
SOPS negative score at baseline		11.5 ± 7.5			
SOPS negative score at follow-up		8.6 ± 6.0			
SOPS total score at baseline		37.5 ± 12.2			
SOPS total score at Follow-up		29.1 ± 13.1			
SAPS total score at baseline			16.9 ± 15.8		
SAPS total score at follow-up			10.4 ± 10.6		
SANS total score at baseline			27.4 ± 13.6		
SANS total score at follow-up			21.8 ± 14.8		
# Medicated/unmedicated at baseline		4/14	12/6		
# Medicated/unmedicated at follow-up		4/14	12/6		
Antipsychotic dose (medicated) at Baseline[d] (mean and range)		12.4 (6.7–150.0)	177.6 (50.0–600.0)	$t = -3.59$	<0.001**
Antipsychotic dose (Medicated) at Follow-up[d] (mean and range)		12.4 (6.7–150.0)	211.1 (25.0–1133.0)	$t = -2.60$	<0.01**

Values are mean ± SD unless otherwise noted. HC = healthy controls; CHR = clinical high risk individuals; FESZ = first episode schizophrenia patients; PSES = parental socioeconomic status, Hollingshead score (1–5 scale, 1 highest); GAF = Global Assessment of Functioning; SOPS = Scale of Prodromal Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms

[a] Annett Handedness Scale total score: 0–2 and writes with right hand = right-handed, 3–9 or writing hand opposite other items = mixed, 10–12 and writes with left hand = left-handed.

[b] Estimated from Reading subtest of Wide Range Achievement Test (WRAT-4).

[c] Estimated from Vocabulary and Block Design subtests of Wechsler Abbreviated Scale of Intelligence (WASI).

[d] Chlorpromazine equivalents calculated using the methods of Stoll (2001) and Woods (2003) for the medicated subgroups only.

* FESZ and CHR showed significantly lower GAF scores compared with HC both at Baseline and Followup (p's < 0.001).

** FESZ had significantly higher medication dose compared with CHR both at Baseline and Followup (p's < 0.01).

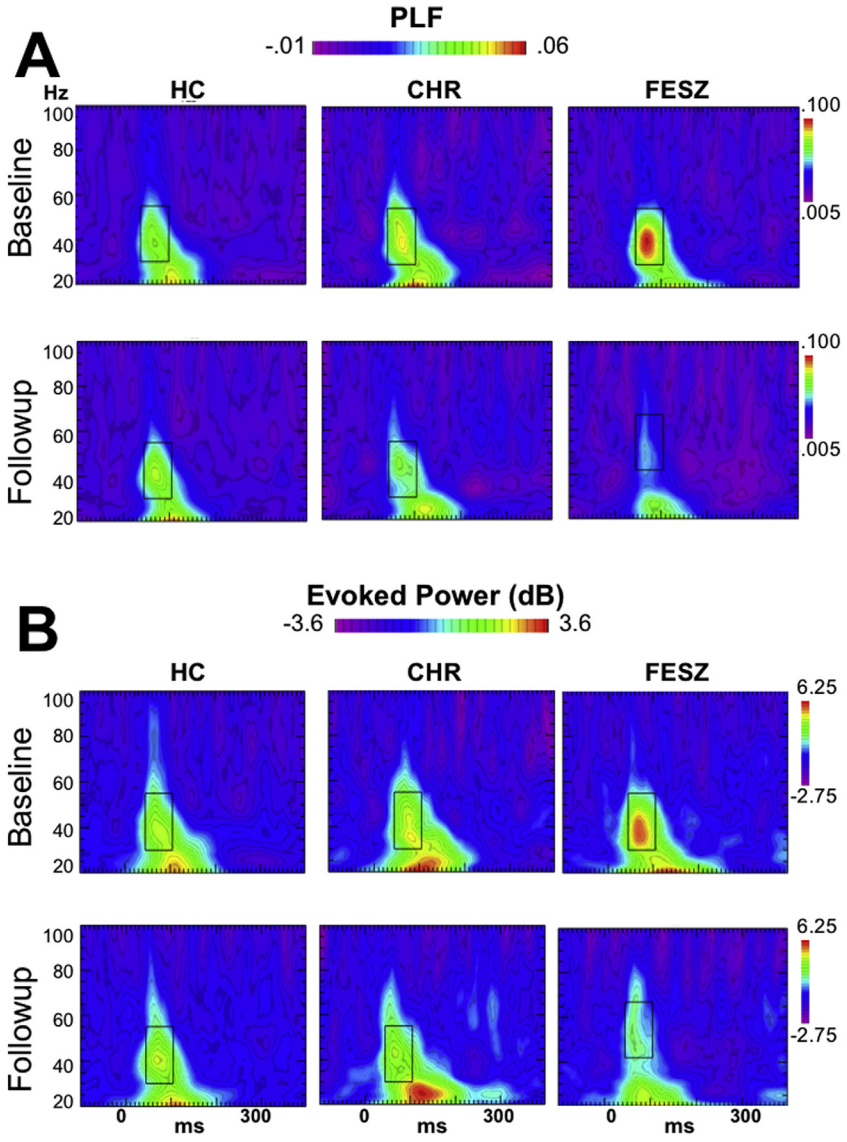

Fig. 1. Early auditory-evoked gamma band response (EAGBR) data. Time-frequency maps of phase locking factor (PLF) (A) and evoked power (B) averaged across all scalp EEG electrodes in healthy controls (HC), clinical high risk individuals (CHR), and first episode schizophrenia patients (FESZ). In each panel, the data at baseline are shown in the top row and at follow-up in the bottom row.

11.80, $p = .001$; temporal: F[1,73] = 11.52, p = .001), and significant Group × Time interactions (fronto-central: F[2,73] = 8.61, $p < .001$; temporal: F[2,73] = 8.43, p = .001). These interactions reflected progressive reductions of EAGBR PLF in FESZ (fronto-central: $t = 3.88$, p = .001, d = 1.08; temporal: $t = 3.55$, $p = .002$, d = 1.13), while HC and CHR did not show significant EAGBR changes over time (HC fronto-central: $t = -0.76$, $p = .45$, d = −0.12; HC temporal: $t = -1.15$, $p = .26$, d = −0.19; CHR fronto-central: $t = 1.25$, $p = .23$, d = 0.25; CHR temporal: $t = 1.51$, $p = .15$, d = 0.30) (Fig. 2, top row). There were no other significant interactions with Group (F's < 1.28, p's > 0.23).

For PLF peak frequency, there was a significant Group × Time interaction (F[2,73] = 4.2, $p = .02$) at temporal sites, which reflected an increase of EAGBR frequency in FESZ from baseline (44.1±4.1 Hz) to follow-up (48.2±4.3 Hz) ($t = -3.0$, $p = .008$). PLF peak frequency did not differ between groups at fronto-central sites.

3.3.2. Evoked power

For the fronto-central EAGBR there was a significant Group × Time interaction (F[2,73] = 7.66, $p = .001$), which was driven by the progressive reduction of evoked power in FESZ ($t = 3.94$, p = .001, d = 1.07). HC and CHR did not show changes over time (HC: $t = -0.48$, $p = .63$, d = −0.07; CHR: $t = 1.12$, $p = .28$, d = 0.21) (Fig. 2, bottom row). There were no significant effects involving Time or Group for the temporal EAGBR (F's < 3.05, p's > 0.09) (Fig. 2, middle row). Evoked power peak frequency did not differ between groups at either set of electrodes.

3.4. ERPs

Please see the Supplemental Text.

4. Discussion

This study compared the EAGBR in CHR, FESZ, and HC groups at baseline and 1-year follow-up assessments. The EAGBR was dissociated into components with fronto-central and temporal topographies by using the average reference method, instead of the average mastoid reference that has been used in most EAGBR studies. The average mastoid reference conflates activity measured at mastoid/lateral temporal and fronto-central electrodes, so the fronto-central and lateral temporal EAGBR components have not generally been dissociated in previous studies of the EAGBR in the schizophrenia spectrum. Here, EAGBR PLF

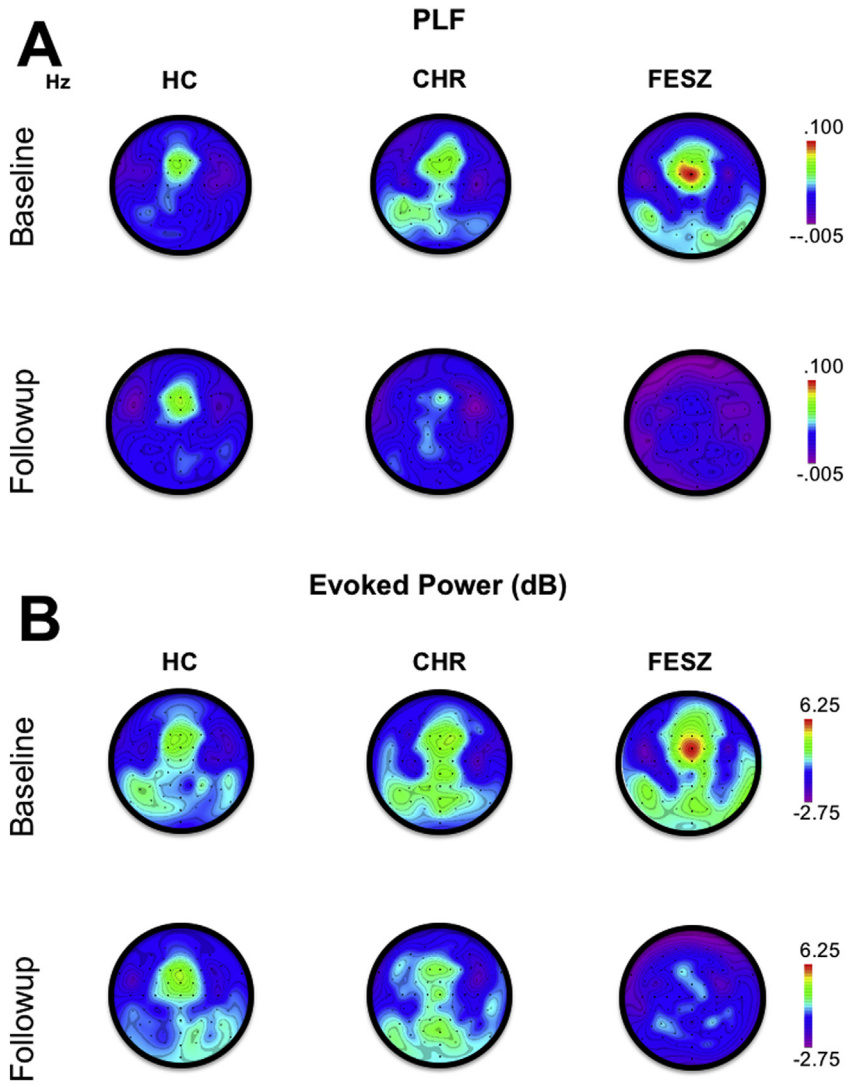

Fig. 2. Maps displaying the topography of average EAGBR PLF and evoked power within the corresponding time-frequency windows in Fig. 1.

and evoked power did not differ between CHR and HC, or between CHR and FESZ, at either assessment interval. Nor did EAGBR PLF or evoked power change over time in HC or CHR. However, in FESZ, we found significant reductions in EAGBR PLF and evoked power over time, at fronto-central and temporal electrodes for PLF and at fronto-central electrodes for evoked power. While FESZ did not differ from HC at baseline, EAGBR PLF was significantly reduced in FESZ at temporal electrodes compared to HC at follow-up. In addition, the frequency of the temporal EAGBR PLF in FESZ increased from baseline to follow-up, and was higher in SZ than HC at follow-up. Thus, we did not find any difference between the groups at baseline, but after one year, EAGBR PLF and evoked power declined in FESZ. (Although there was an outlier [>3 SD] in CHR as seen in Fig. 2, the statistical results reported herein were essentially the same when analyzed without this case.)

The late adolescent to early adulthood period to which the subjects in this study belonged is a vulnerable neurodevelopmental period in which synaptic connectivity and receptor systems, including the *N*-methyl-D-aspartate (NMDA) and GABA receptors, are approaching their adult stages (Catts et al., 2013). This is also the time period in which schizophrenia typically manifests, first with prodromal signs, then later with the onset of psychosis (Lewis and Lieberman, 2000). However, we did not detect any EAGBR abnormalities in CHR individuals. At baseline, the EAGBR appeared to be intact in both CHR and FESZ, but at the one year follow-up, FESZ showed PLF abnormalities in the fronto-central and temporal components of the EAGBR. Thus, we found progressive changes in the EAGBR during the first year following the first hospitalization for psychosis. (Fronto-central EAGBR evoked power also showed a significant reduction over time, although the cross-sectional group difference at follow-up was not significant.) The progressive reduction of the gray matter volume of primary auditory cortex, which we have reported in other FESZ (Kasai et al., 2003), might be also concurrently present, considering that the temporal EAGBR may be generated in the auditory cortex (Mulert et al., 2007; Pantev et al., 1991).

Few studies to date have examined γ oscillations in FESZ. We have previously shown that the γ band ASSR was impaired in FESZ (Spencer et al., 2008). Minzenberg et al. found that γ activity during a working memory task was reduced in both medicated and unmedicated (mostly medication-naïve) FESZ (Minzenberg et al., 2010). Sun et al. reported that medication-naïve FESZ had increased β and low γ activity but decreased high γ in a visual Gestalt perception task (Sun et al., 2013). And, Leicht et al. (2015) and Taylor et al. (2013) found reduced EAGBR evoked power and PLF in FESZ. In contrast, here we did not observe EAGBR abnormalities in FESZ at the baseline assessment, although EAGBR deficits emerged one year later at the follow-up assessment. One possible explanation for the absence of EAGBR deficits at baseline in FESZ is that these individuals had higher premorbid and current IQ than average (see Table 1). We note that FESZ did show a deficit in N1

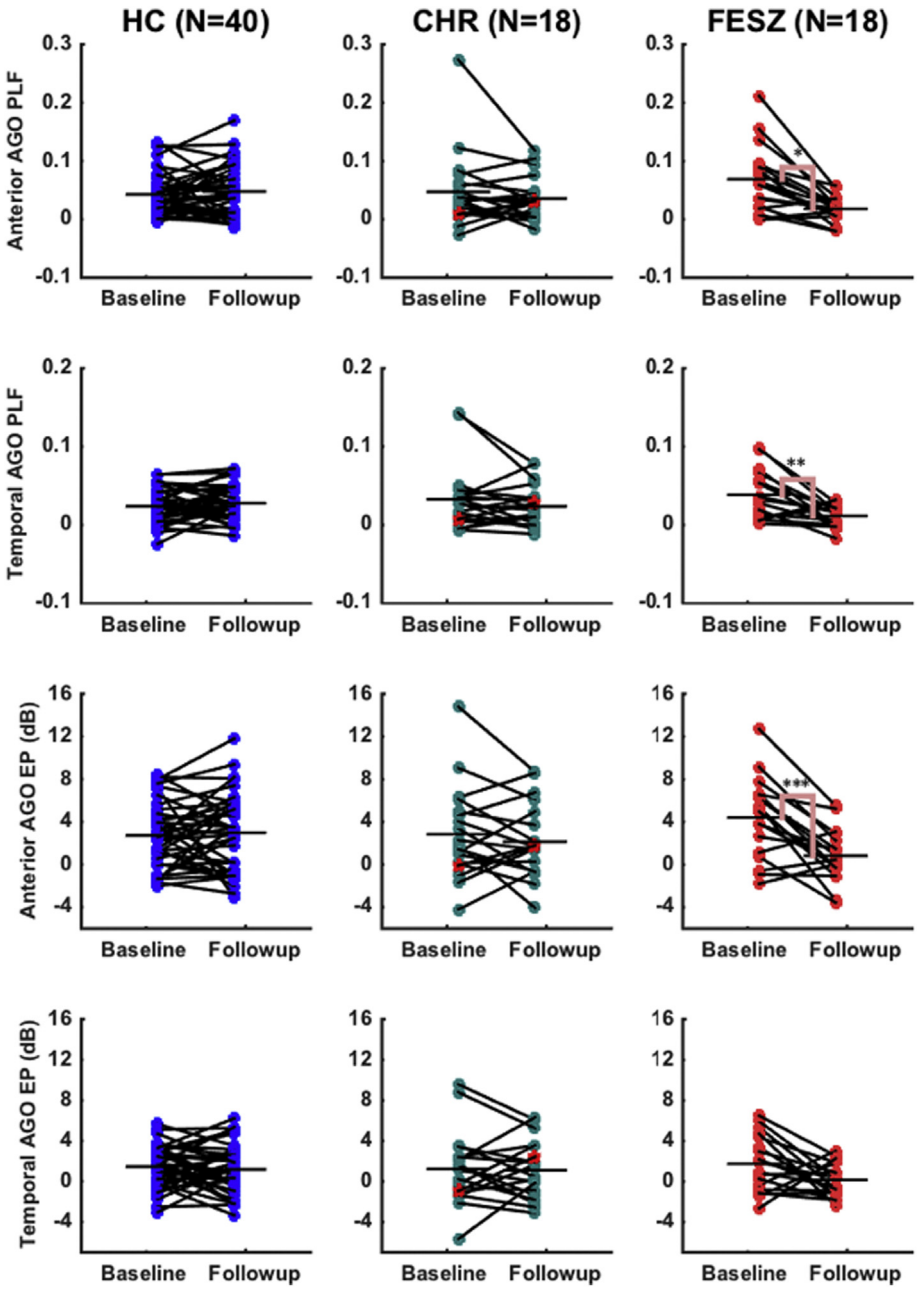

Fig. 3. Scatterplots of the EAGBR data in HC, CHR, and FESZ at baseline and follow-up: fronto-central PLF (top row), temporal PLF (second), fronto-central evoked power (third), and temporal evoked power (bottom). * = significant fronto-central PLF reduction over time ($t[17] = 4.59$, $p < .001$). ** = significant temporal PLF reduction over time ($t[17] = 3.54$, $p = .002$). *** = significant fronto-central evoked power reduction over time ($t[17] = 4.61$, $p < .001$). The converter who was excluded from the analyses is plotted in the CHR data in red.

amplitude (Supplemental Text), consistent with studies of chronic patients (Rosburg et al., 2008), which suggests that this sample was not anomalous.

With regard to CHR, only two other studies of which we are aware have examined γ. Perez et al. (2013) reported a reduction in EAGBR evoked power and a reduction in PLF that did not reach significance. They did not find any differences between CHR who converted to psychosis and those who did not, suggesting that EAGBR deficits reflected neural circuit abnormalities that did not worsen with the onset of psychosis. In the present study we did not find any significant EAGBR abnormalities in CHR at either assessment interval. Given the lack of conversions within the year of follow-up for the sample analyzed, it is possible that this CHR sample was at reduced risk or in an earlier phase of illness than other CHR samples. However, we note that the CHR here had nearly the same mean SOPS total scores (37.8 ± 11.8 at baseline) as those in the Perez et al. study (37.4 ± 15.6), so a difference in symptom severity is unlikely to be the cause of these discrepant results. In a study of the ASSR in CHR and FESZ, Tada et al. (2016) reported reductions of 40 Hz ASSR PLF and power in CHR and FESZ, although the ASSR is a different oscillation. One possibility is that our CHR sample had higher IQs than the population average, so our group may have been atypical. (The CHR participants' IQ in Perez et al. was not reportEd.) The extent of EAGBR deficits in CHR individuals remains to be determined.

In summary, we found that the fronto-central and temporal components of the EAGBR were differentially affected in the early course of schizophrenia, and showed progressive declines over the course of one year. These patterns may reflect the abnormal maturation of γ generating circuits in frontal and temporal cortical areas. In contrast, the EAGBR was not affected in CHR individuals.

Conflict of interest

All authors declare that they have no conflicts of interest arising from this manuscript.

Contributors

All persons designated as authors qualify for authorship as each author substantially contributed to the study by either being involved in the study conception and design (LJS, RMG, KAW, JDW, MES, JMG, MAN, RWM, KMS), acquisition of data (NO, YH, EdR), data analysis (NO, YH, KMS), writing (NO, KMS), or contributed to discussion and revising of the manuscript for intellectual content (all authors). All persons that were involved in the preparation of this manuscript are listed as authors.

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Appendix A. Supplementary data

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