Spontaneous Gamma Activity in Schizophrenia

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**IMPORTANCE** A major goal of translational neuroscience is to identify neural circuit abnormalities in neuropsychiatric disorders that can be studied in animal models to facilitate the development of new treatments. Oscillations in the gamma band (30-100 Hz) of the electroencephalogram have received considerable interest as the basic mechanisms underlying these oscillations are understood, and gamma abnormalities have been found in schizophrenia (SZ). Animal models of SZ based on hypofunction of the N-methyl-D-aspartate receptor (NMDAR) demonstrate increased spontaneous broadband gamma power, but this phenomenon has not been identified clearly in patients with SZ.

**OBJECTIVE** To examine spontaneous gamma power and its relationship to evoked gamma oscillations in the auditory cortex of patients with SZ.

**DESIGN, SETTING, AND PARTICIPANTS** We performed a cross-sectional study including 24 patients with chronic SZ and 24 matched healthy control participants at the Veterans Affairs Boston Healthcare System from January 1, 2009, through December 31, 2012. Electroencephalograms were obtained during auditory steady-state stimulation at multiple frequencies (20, 30, and 40 Hz) and during a resting state in 18 participants in each group.

**MAIN OUTCOMES AND MEASURES** Electroencephalographic activity in the auditory cortex was estimated using dipole source localization. Auditory steady-state response (ASSR) measures included the phase-locking factor and evoked power. Spontaneous gamma power was measured as induced (non–phase-locked) gamma power in the ASSR data and as total gamma power in the resting-state data.

**RESULTS** The ASSR phase-locking factor was reduced significantly in patients with SZ compared with controls for the 40-Hz stimulation (mean [SD], 0.075 [0.028] vs 0.113 [0.065]; $F_{1,46} = 6.79$ [$P = .012$]) but not the 20- or the 30-Hz stimulation (0.042 [0.038] vs 0.043 [0.034]; $F_{1,46} = 0.006$ [$P = .938$] and 0.084 [0.040] vs 0.098 [0.050]; $F_{1,46} = 1.605$ [$P = .212$], respectively), repeating previous findings. The mean [SD] broadband-induced (30-100 Hz) gamma power was increased in patients with SZ compared with controls during steady-state stimulation (6.579 [3.783] vs 3.984 [1.843]; $F_{1,46} = 9.128$ [$P = .004$]; $d = 0.87$) but not during rest (0.006 [0.003] vs 0.005 [0.002]; $F_{1,46} = 1.067$ [$P = .309$]; $d = 0.35$). Induced gamma power in the left hemisphere of the patients with SZ during the 40-Hz stimulation was positively correlated with auditory hallucination symptoms (tangential, $p = 0.587$ [$P = .031$]; radial, $p = 0.593$ [$P = .024$]) and negatively correlated with the ASSR phase-locking factor (baseline: $p = −0.572$ [$P = .024$]; ASSR: $p = −0.568$ [$P = .032$]).

**CONCLUSIONS AND RELEVANCE** Spontaneous gamma activity is increased during auditory steady-state stimulation in SZ, reflecting a disruption in the normal balance of excitation and inhibition. This phenomenon interacts with evoked oscillations, possibly contributing to the gamma ASSR deficit found in SZ. The similarity of increased spontaneous gamma power in SZ to the findings of increased spontaneous gamma power in animal models of NMDAR hypofunction suggests that spontaneous gamma power could serve as a biomarker for the integrity of NMDARs on parvalbumin-expressing inhibitory interneurons in humans and in animal models of neuropsychiatric disorders.

A major goal of translational neuroscience is to identify neural circuit abnormalities in neuropsychiatric disorders that can be studied in animal models to facilitate the development of new treatments. Oscillations in the gamma band (30-100 Hz) of the electroencephalogram (EEG) have received considerable interest in this effort because the basic mechanisms underlying these oscillations are understood and are believed to be conserved across species. Schizophrenia (SZ) is characterized by abnormalities in gamma oscillations elicited by a variety of stimuli and tasks, particularly deficits in the auditory steady-state response (ASSR) to gamma frequency stimulation. Dysfunctional gamma oscillations have been proposed to be caused by abnormalities in parvalbumin (PV)-expressing fast-spiking basket cells (PVBCs). The PVBCs are a critical element in neural circuits that generate gamma oscillations, and neuropathological studies have demonstrated abnormalities in PVBCs in SZ.

Hypofunction of the N-methyl-D-aspartate receptor (NMDAR) has been proposed to be an important factor in the pathophysiological features of SZ. In awake and behaving rodents, NMDAR antagonism induces behavioral and psychophysiological abnormalities resembling those found in SZ and increased spontaneous (non-stimulus-locked) broadband gamma activity. This effect may be caused by the reduction of NMDAR function on PV-expressing interneurons because mice with genetic reductions of NMDAR function on PV-expressing interneurons also exhibit increased spontaneous gamma activity.

For gamma oscillations to be useful as biomarkers of PVBC-mediated inhibition, correspondences must be found between gamma alterations in neuropsychiatric disorders and in animal models of these disorders. However, most reported gamma abnormalities in patients with SZ are characterized by reduced power and/or phase synchronization, whereas spontaneous gamma power is increased in animal models of NMDAR hypofunction. Two studies suggest that the latter phenomenon also may occur in an awake and stimulated state in patients with SZ. Teale et al found that induced (non-phase-locked) 40-Hz power during the ASSR to 40-Hz stimuli was increased in patients with SZ compared with controls. Spencer reported increased baseline 40-Hz power during 40-Hz auditory steady-state stimulation in patients with SZ. However, no study, to our knowledge, has demonstrated an increase in spontaneous broadband gamma oscillations in SZ as in animal models of NMDAR hypofunction.

In our study, we examine whether spontaneous gamma power in patients with chronic SZ differed from that of healthy control participants at rest and during auditory steady-state stimulation at multiple frequencies. We tested whether (1) broadband spontaneous gamma power was increased in SZ, (2) spontaneous gamma power was related to deficits in stimulus-evoked activity in SZ, and (3) spontaneous gamma power was related to psychotic symptoms, such as hallucinations.

Methods

The institutional review boards of the Veterans Affairs Boston Healthcare System and Harvard Medical School approved this study. After a detailed description of the study, each participant gave written informed consent. Details of the participants’ demographic and clinical characteristics are given in eTable 1 and eTable 2 in the Supplement. Recruitment and characterization of participants, stimuli and procedures, EEG recording and processing methods, source localization, and spectral analyses are described in the eAppendix in the Supplement. The final sample of participants consisted of 24 controls and 24 patients with SZ who underwent EEG recording while listening to auditory steady-state stimuli (20, 30, and 40 Hz) and during rest (18 controls and 18 patients with SZ).

The ASSR sources were localized with a 4-dipole model consisting of tangential and radial pairs of dipoles in the superior temporal plane of each hemisphere (Figure 1). This dipole model was applied to the induced power and resting EEG data. The ASSR was measured with the phase-locking factor (PLF) and evoked power. Spontaneous gamma activity in the ASSR data was measured as induced power during the baseline (~500 to 0 milliseconds) and the ASSR (30-530 milliseconds) periods. We calculated the mean PLF and evoked power within the time window (30-530 milliseconds) and the frequencies (20 Hz: 20-22 Hz; 30 Hz: 30-33 Hz; and 40 Hz: 40-44 Hz) at which the ASSR was maximal. The frequency range of 30 to 100 Hz was used for the baseline, ASSR-induced, and resting-state power analyses (excluding 60 Hz owing to power line artifacts). Corrections for multiple tests used the Bonferroni method.

For statistical analysis of ASSR PLF and evoked power data, analyses of variance used the following design: group (SZ/controls) × stimulation frequency (20-Hz/30-Hz/40-Hz) × hemisphere (left/right) × dipole (tangential/radial). Induced γ analyses also included the factor time period (pre-stimulus baseline/period of the ASSR). For resting-state γ data, analyses of variance used the following design: group (SZ/controls) × hemisphere (left/right) × dipole (tangential/radial). The Greenhouse-Geisser correction for inhomogeneity of variance was applied for factors with more than 2 levels and is reflected in the reported P values.

Effect sizes are expressed as Cohen d. The nonparametric Spearman ρ was used for correlation analyses. All statistical tests were 2-tailed with α = .05.

Results

ASSR PLF and Evoked Power

The ASSR PLF was reduced in patients with SZ compared with controls overall (mean [SD], 0.067 [0.024] vs 0.085 [0.034]; F1,46 = 4.36 [P = .042]) (Figure 2). This deficit varied between stimulation frequencies and hemispheres (group × frequency × hemisphere interaction: F1,46 = 3.36 [P = .039]). The ASSR PLF did not differ between groups for the 20-Hz (mean [SD], 0.042 [0.038] vs 0.043 [0.034]; F1,46 = 0.006 [P = .938]) and 30-Hz (0.084 [0.040] vs 0.099 [0.050]; F1,46 = 1.605 [P = .212]) conditions. In the 40-Hz condition, we found a significant main effect of group (mean [SD], 0.075 [0.028] vs 0.113 [0.065]; F1,46 = 6.79 [P = .012]) and a significant group × hemisphere interaction (F1,46 = 4.31 [P = .043]). The ASSR PLF was reduced in patients with SZ compared with controls for the left hemisphere dipoles (mean [SD], 0.057 [0.037] vs 0.110 [0.065]; t46 = 3.46 [P = .002, corrected]; d = 1.00) but not for the right
hemisphere dipoles (0.093 [0.045] vs 0.115 [0.072]; \( t_{46} = 1.31 \) \( P = .296 \), corrected; \( d = 0.38 \)). The PLF was reduced in patients with SZ for the left hemisphere radial (mean [SD], 0.056 [0.041] vs 0.111 [0.077]; \( t_{46} = 3.07 \), \( P = .007 \) corrected, \( d = 0.89 \)) and tangential dipoles (0.059 [0.056] vs 0.110 [0.078]; \( t_{46} = 2.62 \) [\( P = .02 \), corrected]; \( d = 0.76 \)). The ASSR-evoked power did not differ between groups (mean [SD], 5.235 [3.243] vs 5.51 [2.923]; \( F_{1,46} = 0.88 \), \( P = .396 \), corrected; \( d = 0.38 \)). The ASSR-evoked power did not differ between groups (mean [SD], 5.235 [3.243] vs 5.51 [2.923]; \( F_{1,46} = 0.88 \), \( P = .396 \), corrected; \( d = 0.38 \)). The ASSR-evoked power did not differ between groups (mean [SD], 5.235 [3.243] vs 5.51 [2.923]; \( F_{1,46} = 0.88 \), \( P = .396 \), corrected; \( d = 0.38 \)). The ASSR-evoked power did not differ between groups (mean [SD], 5.235 [3.243] vs 5.51 [2.923]; \( F_{1,46} = 0.88 \), \( P = .396 \), corrected; \( d = 0.38 \)).

The ASSR-induced gamma power was increased in the patients with SZ compared with the controls in the 20-Hz (6.940 [4.755] vs 4.015 [2.205]; \( F_{1,46} = 7.475 \) [\( P = .009 \), corrected; \( d = 0.76 \)]) and 30-Hz (6.668 [3.657] vs 4.211 [2.775]; \( F_{1,46} = 6.876 \) [\( P = .012 \), corrected; \( d = 0.76 \)]) conditions. For the 40-Hz stimulation, induced gamma power was increased in the patients with SZ compared with the controls (6.256 [4.501] vs 3.909 [2.205]; \( F_{1,46} = 5.250 \) [\( P = .027 \), corrected; \( d = 0.66 \]), and this effect differed according to hemisphere (group \( \times \) hemisphere interaction: \( F_{1,46} = 9.078 \) [\( P = .048 \), corrected; \( d = 0.89 \) but not the right hemisphere dipoles (6.144 [4.449] vs 4.689 [3.508]; \( t_{46} = 1.258 \) [\( P = .23 \), corrected; \( d = 0.36 \)]).

Thus, in the baseline period, induced gamma power was increased in the patients with SZ in both hemispheres for the 20- and 30-Hz stimulations and in the left hemisphere only for the 40-Hz stimulation.

During the ASSR period, induced gamma power was increased in patients with SZ in the left hemisphere dipoles (6.368 [5.063] vs 3.128 [1.419]; \( t_{46} = 3.019 \) [\( P = .008 \), corrected; \( d = 0.89 \)]) but not the right hemisphere dipoles (6.144 [4.449] vs 4.689 [3.508]; \( t_{46} = 1.258 \) [\( P = .23 \), corrected; \( d = 0.36 \)]. Although this effect did not vary between stimulation frequencies and hemispheres (group \( \times \) frequency \( \times \) hemisphere interaction: \( F_{1,46} = 9.078 \) [\( P = .048 \), corrected; \( d = 0.89 \)]) but not the right hemisphere dipoles (6.144 [4.449] vs 4.689 [3.508]; \( t_{46} = 1.258 \) [\( P = .23 \), corrected; \( d = 0.36 \)].

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left hemisphere dipoles (5.896 [4.180] vs 3.501 [1.909]; $t_{46} = -2.854 [P = .036, corrected]; d = 0.75) than in the right hemisphere dipoles (6.716 [5.811] vs 4.181 [2.675]; $t_{46} = -1.941 [P = .35, corrected]; d = 0.56) in the patients with SZ.

Resting-State Gamma Power
In contrast to induced gamma power during the ASSR task, we found no significant overall group difference in resting-state gamma power (0.006 [0.003] vs 0.005 [0.002]; $F_{3,38} = 1.067 [P = .309]; d = 0.35) (Figure 4A) and no significant interactions of group with other factors ($Fs < 1.674 [Ps > .204]$). Resting gamma power was not correlated with induced gamma power in controls or in the patients with SZ (eAppendix in the Supplement).

Correlations Between Induced Gamma Power and Auditory Hallucination Symptoms
Previous investigations$^{21,22}$ found positive correlations between auditory hallucination symptom ratings and gamma ASSR PLF. Therefore, we examined whether the 40-Hz ASSR PLF in the left hemisphere, induced gamma power, and resting-state gamma power in the patients with SZ were correlated with the auditory hallucinations rating in the Scale for the Assessment of Positive Symptoms.$^{23}$ The 40-Hz ASSR PLF was not correlated with auditory hallucinations (left hemisphere tangential: $\rho = 0.225 [P = .29, uncorrected]$; left hemisphere radial: $\rho = -0.246 [P = .25, uncorrected]$). The mean induced gamma power was calculated for the baseline and ASSR periods and tested for each hemisphere, dipole, and stimulation frequency (Bonferroni correction: 2 hemispheres × 2 dipoles × 3 frequencies). The left hemisphere tangential and radial dipole-induced gamma power during the 40-Hz stimulation were positively correlated with auditory hallucinations ($\rho = 0.587 [P = .031]$ and $\rho = 0.593 [P = .024]$, respectively). No other correlations were significant ($-0.056 < \rho < 0.401, [P > .624]$) (Figure 4B). Resting gamma power was not correlated with auditory hallucinations ($\rho < 0.334 [P > .175, uncorrected]$).

Correlations Between Induced Gamma Power and ASSR PLF/Evoked Power at 40 Hz
To test whether increased induced gamma power was related to the 40-Hz ASSR PLF deficit in SZ, induced gamma power at 40 Hz was correlated with the 40-Hz ASSR PLF for each dipole in the

Figure 2. Time Frequency Maps of Evoked Gamma Oscillations in the Auditory Cortex

| Time frequency map of cortical dipole source activities for the 20-, 30-, and 40-Hz auditory steady-state response (ASSR) for healthy control participants (HC) and patients with schizophrenia (SZ). A, Color scale indicates phase-locking factor (PLF) values. B, Color scale indicates power values in microvolts squared. RH indicates right hemisphere.

* Left hemisphere (LH) tangential and radial ASSR PLF during the 40-Hz stimulation were significantly reduced in patients with SZ.
baseline and ASSR periods. In general, the PLF tended to show negative correlations with prestimulus- and poststimulus-induced gamma power in both groups. After Bonferroni correction (2 dipoles × 2 hemispheres × 2 subject groups × 2 time periods), the only significant correlations between induced gamma power and the PLF were for the left hemisphere radial dipole in the baseline and ASSR periods in the patients with SZ (baseline: \( \rho = -0.572 \ [P = .024] \); ASSR: \( \rho = -0.568 \ [P = .032] \)) and in the ASSR period in the controls (\( \rho = -0.554 \ [P = .040] \)) (Figure 4C).

For the 40-Hz ASSR-evoked power, we found no correlations with the 40-Hz induced gamma power in the controls (\( -0.088 < \rho < 0.261 \ [P > .218, \text{uncorrected}] \)). In the patients with SZ, the correlations were all positive, but none remained significant after Bonferroni correction (as for the PLF above) (\( 0.070 < \rho < 0.560 \ [P > .064] \)).

Correlations Between Gamma Measures and Antipsychotic Medication Dosage
No correlations with antipsychotic dosage were found. Details are provided in the eAppendix in the Supplement.

Discussion

Gamma ASSR Deficit in SZ
Consistent with previous studies, the ASSR PLF was reduced for the 40-Hz stimulation in the patients with SZ compared with the controls but was not reduced or was less affected at lower stimulation frequencies. Thus, the basic finding of a deficit in gamma frequency synchronization in the auditory cortex in SZ was reproduced here. The 40-Hz ASSR PLF deficit was lateralized to the left hemisphere, similar to some previous findings. However, the 40-Hz ASSR-evoked power was not decreased in SZ, in contrast to most reports. The reason for this discrepancy is not clear, but similar patterns of gamma PLF deficits without evoked power deficits in SZ have been reported. One explanation is that the factors involved in increasing spontaneous gamma power might also increase evoked gamma power and counteract an evoked power reduction. Lazarewicz et al found that ketamine increased spontaneous gamma and evoked gamma power to tones in rats, and Spencer reported a correlation between baseline power and ASSR-evoked power. Providing some support for this hypothesis, the 40-Hz ASSR-evoked power and induced gamma power in SZ tended to be positively correlated here, but none of the correlations reached significance after strict Bonferroni correction.

Increased Spontaneous Gamma Activity in SZ
We measured spontaneous gamma activity as induced gamma power in the ASSR task and total gamma power during rest. We found that broadband (30-100 Hz) spontaneous gamma power was increased overall in the patients with SZ compared with the controls in the baseline and ASSR periods regardless of the frequency of steady-state stimulation. This study thus confirms and extends the earlier reports of increased spontaneous gamma power during the 40-Hz auditory stimulation task.
torysteady-statestimulationinSZ.Spencer 19foundthattotal
40-Hzpowerwasincreasedintheleftauditorycortexduring
the baseline period, with a trend for increased broadband
gamma power. Teale et al18 found increased 40-Hz induced
power during the 40-Hz ASSR. In the present study, with a
larger sample size than that of Spencer,19 we found that in-
creased spontaneous gamma activity was a broadband phe-
nomenon and not specific to the stimulation frequency. Fur-
thermore, spontaneous gamma activity was increased during
the baseline and ASSR periods (and was highly correlated be-
tween these periods; see the eAppendix in the Supplement).

However, spontaneous gamma power was not increased in
SZ during rest. Although the effect size ($d = 0.35$) suggests a weak
effect that could become significant with a larger sample size, a
recent study29 with a very large sample failed to find increased
gamma power during rest. Furthermore, we did not find a cor-
relation between resting and induced gamma power. This disso-
ciation may have been found because cortical gamma activity is
increased during wakefulness compared with rest, an effect that
involves activation of the mesencephalic reticular formation and
cholinergic input to the cortex from the basal forebrain.30,31 In-
creased spontaneous gamma activity in SZ may require this choli-
ergic input to occur or to be amplified to a detectable level.

An important question is whether increased spontaneous
gamma activity in SZ occurred in the same or in different neural
circuitry as that which generates the ASSR. As noted above,
the 40-Hz ASSR PLF was decreased in the left hemisphere of
the patients with SZ without a concomitant decrease in evoked
power, and the typical correlation between ASSR-evoked power
and the PLF was absent in the patients with SZ in the left hemi-
sphere during the 40-Hz stimulation. One explanation for this
pattern of results is that increased spontaneous gamma activity
occurred in the same circuit that generates the ASSR, but the
higher level of intrinsic activity prevented the circuit from syn-
chronizing to the steady-state stimulus. However, if this were
the case, increased spontaneous gamma power should have
been correlated with the PLF and evoked power reductions, but
we did not observe this pattern. Another possibility is that the
reduction of the 40-Hz ASSR PLF in the left hemisphere of
the patients with SZ could have resulted from an increase in over-
lapping spontaneous gamma power, which could have dis-
rupted the PLF measure without altering the actual ASSR. In sig-

![Figure 4. Resting-State Power and Correlations With Induced Gamma Power](https://jamanetwork.com/)

A, Resting-state power spectra of dipole-source activities for healthy
control participants and patients with schizophrenia. Shaded color bands
indicate 95% CIs; gray areas, gamma band (30-100 Hz). B, Correlations
between the auditory hallucination symptom score (0 indicates no
history; 5, a high propensity for experiencing auditory hallucinations)
and induced gamma power in the left hemisphere (LH) during 40-Hz
stimulation in patients with schizophrenia. C, Correlations
between induced gamma power in the radial LH (baseline and auditory
steady-state response [ASSR] periods) at 40 Hz and the radial LH
ASSR phase-locking factor (PLF) at 40 Hz during the 40-Hz stimulation.

* Only correlations with Bonferroni-corrected $P < .05$ are indicated.
some previous studies, positive correlations between the and differences between task conditions or participant groups and thus reports of increased intrinsic neural activity and cortical present findings support this hypothesis and complement icsof these spontaneous gamma activity.

The broadband nature of the increased spontaneous gamma effect raises the question of whether true oscillatory activity was affected. Rather, this effect could represent an increase in random noise in the gamma band. A resolution of this question will require detailed analyses of the dynamics of the spontaneous gamma activity.

Increased Intrinsic Neural Activity in SZ
In SZ, induced gamma power in left hemisphere sources was positively correlated with auditory hallucination symptoms for the 40-Hz but not for the other stimulation frequencies. This finding is consistent with many reports of relationships between auditory hallucinations and left auditory cortex structure and function. Thus, greater gamma power was associated with an increase in this aspect of psychosis. The direction of this abnormality goes against the common assumption that SZ should be associated only with decreased gamma-band activity. In some previous studies, positive correlations between the PLF of particular beta and gamma oscillations and psychotic symptoms, including hallucinations, have been found despite sometimes finding group-level reductions in the PLF (although we did not replicate previous findings of correlations between auditory hallucination symptoms and the ASSR PLF here). These findings led to a proposal that psychosis could involve increased high-frequency oscillatory activity. The present findings support this hypothesis and complement reports of increased intrinsic neural activity and cortical excitability in particular brain regions in SZ.

Possible Confounds by Artifacts
The high- and low-frequency bands of the EEG are susceptible to particular types of physiological artifacts, such as electromyographic and electro-oculographic activity, which can differ between task conditions or participant groups and thus masquerade as experimentally induced oscillation effects. These confounds appear to affect only measures of non–phase-locked activity. Thus, increased spontaneous gamma power in SZ simply could have been caused by a greater degree of artifact contamination in the patients’ EEGs. We attempted to minimize this possibility by (1) identifying artifacts in the scalp EEGs and removing them using independent component analysis, the present state-of-the-art method for artifact removal, and (2) using source localization as a spatial filter to focus on auditory cortex activity, a method that also reduces contamination by noise at the scalp electrode level. (Previous investigations of EEG noise in SZ have not used these methods to reduce contamination by artifacts, so the validity of their findings is not clear.) Although the possibility of residual noise cannot be excluded, the increased spontaneous gamma effect was modulated by the factors of stimulation frequency, period, and hemisphere. Furthermore, spontaneous gamma power was correlated with auditory hallucination symptoms only in the left hemisphere for the 40-Hz stimulation. Thus, artifacts are unlikely to explain the pattern of increased spontaneous gamma effects found here.

Neural Circuit Basis of Increased Spontaneous Gamma Power
One explanation for increased induced gamma power in SZ is an alteration in the balance of excitation and inhibition in the auditory cortex via the disinhibition of pyramidal cells by reduced PVBC activity. This disinhibition could come about by a reduction in PVBC firing from reduced function of NMDARs on PVBCs because NMDAR hypofunction is implicated in SZ. Evidence of reduced expression of NMDARs on PV-expressing inhibitory interneurons in SZ exists. In rodents, pyramidal cell excitability and spontaneous gamma power are increased by NMDAR antagonists. The genetic reduction of NMDAR function on PV-expressing interneurons also increases excitability and spontaneous gamma power. Likewise, in humans, ketamine increased the power of an auditory-evoked gamma oscillation and motor cortex excitability. Computational modeling suggests that a reduction of NMDAR input to fast-spiking interneurons could increase gamma power by improving the ability of interneurons to track fast inputs. We note that increased activity could also result from other mechanisms, as demonstrated by studies involving the global downregulation of NMDAR subunit NR1 expression, deletion of the neuregulin receptor ErbB4 on PV-expressing interneurons, microdeletion, and dopamine D<sub>1</sub> receptor agonism.

Translational Implications and Caveats
These results demonstrate that induced gamma activity is increased in patients with chronic SZ during awake listening to steady-state stimuli but not during rest. The similarity of this induced gamma effect to the findings of increased spontaneous gamma activity in animal models of NMDAR hypofunction suggests that induced gamma activity could serve as a biomarker for the integrity of NMDARs on PVBCs in humans and in animal models of neuropsychiatric disorders (although other mechanisms could be involved, as noted above). Because induced gamma activity was related to auditory hallucination symptoms, the reduction of induced gamma activity by increasing PVBC inhibitory output could lead to the amelioration of psychotic symptoms.

Some caveats of this study should be noted. First, the patients with SZ had used atypical antipsychotics for many years, as in most studies of SZ, so the degree to which medication influences the present findings can be accounted for by correlating effects with chlorpromazine equivalents is unknown.
Second, the active behavioral state of rodents in most of the model studies of NMDAR hypofunction differed from the passive listening state of the human participants during the ASSR recording. The degree to which this difference in state might influence spontaneous gamma activity is unknown.

Conclusions

We found that spontaneous gamma activity is increased during auditory steady-state stimulation in patients with SZ, reflecting a disruption in the normal balance of excitation and inhibition. This phenomenon interacts with evoked oscillations, possibly contributing to the gamma ASSR deficit found in SZ. The similarity of increased spontaneous gamma power in SZ to the findings of increased spontaneous gamma power in animal models of NMDAR hypofunction suggests that spontaneous gamma power could serve as a biomarker for the integrity of NMDARs on PV-expressing inhibitory interneurons in humans and in animal models of neuropsychiatric disorders.

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Study concept and design: Hirano, Onitsuka, Spencer.

Acquisition, analysis, or interpretation of data: Hirano, Onibe, Kanba, Nestor, Spencer.

Drafting of the manuscript: Hirano, Onibe, Onitsuka, Spencer.

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Correction: This article was corrected on January 21, 2015, to fix the Results portion of the Abstract.

REFERENCES


52. Homaoyun H, Moghaddam B. NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. *J Neurosci*. 2007;27(43):11496-11500.


