



Stimulus train duration but not attention moderates γ -band entrainment abnormalities in schizophrenia



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ABSTRACT

Electroencephalographic (EEG) studies of auditory steady-state responses (aSSRs) non-invasively probe gamma-band (40-Hz) oscillatory capacity in sensory cortex with high signal-to-noise ratio. Consistent reports of reduced 40-Hz aSSRs in persons with schizophrenia (SZ) indicate its potential as an efficient biomarker for the disease, but studies have been limited to passive or indirect listening contexts with stereotypically short (500 ms) stimulus trains. An inability to modulate sensorineural processing in accord with behavioral goals or within the sensory environmental context may represent a fundamental deficit in SZ, but whether and how this deficit relates to reduced aSSRs is unknown. We systematically varied stimulus duration and attentional contexts to further mature the 40-Hz aSSR as biomarker for future translational or mechanistic studies. Eighteen SZ and 18 healthy subjects (H) were presented binaural pure-tones with or without sinusoidal amplitude modulation at 40-Hz. Stimulus duration (500-ms or 1500-ms) and attention (via a button press task) were varied across 4 separate blocks. Evoked potentials recorded with dense-array EEGs were analyzed in the time-frequency domain. SZ displayed reduced 40-Hz aSSRs to typical stimulation parameters, replicating previous findings. In H, aSSRs were reduced when stimuli were presented in longer trains and were slightly enhanced by attention. Only the former modulation was impaired in SZ and correlated with sensory discrimination performance. Thus, gamma-band aSSRs are modulated by both attentional and stimulus duration contexts, but only modulations related to physical stimulus properties are abnormal in SZ, supporting its status as a biomarker of psychotic perceptual disturbance involving non-attentional sensori-cortical circuits.

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1. Introduction

The generation of spatially coherent neural oscillations in the gamma-band (25–120-Hz) is believed necessary for establishing synchrony in local cell ensembles and carrying out essential cerebral cortical computations (Buzsaki, 2009; Uhlhaas and Singer, 2010). Gamma oscillations depend on local GABA-ergic interneuronal coordination (Gonzalez-Burgos and Lewis, 2008; Traub et al., 2004) and their disruption is hypothesized to link global cellular abnormalities in SZ (Curley and Lewis, 2012) to perceptual (Uhlhaas et al., 2006) and cognitive deviations prevalent in the disorder (Basar-Eroglu et al., 2007). Though externally and internally driven gamma oscillations are detectable and quantifiable at the scalp in humans with electro- and magnetoencephalography (E/MEG), the presence or nature of basic sensori-cortical gamma-band abnormalities in SZ

exhibit inconsistency, including augmentations, reductions, and null effects across studies (Clementz and Blumenfeld, 2001; Hall et al., 2010; Hamm et al., 2012a; Moran and Hong, 2011; Spencer et al., 2004).

Auditory stimuli presented at a constant and rapid rate elicit steady-state responses (aSSRs), or sustained auditory neural entrainment, in the listener. Human aSSRs measured with E/MEG exhibit specific resonance in mid gamma-band frequencies [30–50-Hz, i.e. a stimulus every 20–33 ms (Galambos et al., 1981; Picton et al., 2003)], theoretically reflecting the propensity of cortical networks to oscillate in this frequency range (Brenner et al., 2009). Importantly, the 40-Hz aSSR exhibits enhanced signal-to-noise ratio versus background and transient gamma oscillations, affording a powerful tool in assessing the integrity of gamma-generating cortical circuitry.

Aside from the fact that hallucinations specifically in the auditory domain are a characteristic feature of SZ (Goodwin et al., 1971) and other psychoses (Baethge et al., 2005), SZ also typically display deficiencies in basic auditory processing and feature discrimination which are independent of higher-level cognitive dysfunction (Rabinowicz et al., 2000) and may reflect core pathology (Javitt and Freedman, 2015;

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Javitt, 2009). While it is known that both positive and negative symptomology covary with gamma-band aSSR magnitude (Hamm et al., 2011; Hirano et al., 2015), an understanding of the relationship between aSSR and basic auditory processing abnormalities has not been established in SZ. Because auditory processing is by nature a temporally precise modality and more sensitive to time perception abnormalities in SZ than e.g. vision (Carroll et al., 2008b), it follows that discordant neuronal synchrony at rapid timescales, such as the gamma aSSR, could theoretically relate to auditory perceptual difficulties.

A majority [at least 11 out of 14; see Brenner et al. (2009)] of investigations of 40-Hz aSSRs in SZ indicate reduction of entrainment related to the disease which is bilateral in auditory cortex (when measured with MEG; Oda et al., 2012; Teale et al., 2008; Vierling-claassen et al., 2008a, 2008b). The fact that different results also come from studies with different stimulus parameters is noteworthy. Hamm et al. (2011) demonstrated normal 40-Hz aSSRs in left hemisphere in SZ when stimulus trains were actively attended. Hamm et al. (2012b) showed augmented 40-Hz aSSRs with EEG during passive listening, and both studies utilized stimulus trains 2–3 times longer than most aSSR SZ reports. This pattern could suggest that SZ gamma abnormalities do not reflect a pure gamma generation deficit per se, but, rather, deficient interaction of sensory processing with environmental and/or behavioral context.

Interestingly, in psychiatrically healthy subjects (H) allocation of attention to 40-Hz auditory stimulus trains enhances aSSR amplitude (Ross et al., 2004; Saupe et al., 2009), although insufficient task difficulty may eliminate this relatively small effect (Griskova-Bulanova et al., 2011). The influence of attention on aSSR amplitude is unknown in SZ. The specific impact of stimulus train duration on aSSRs is far less frequently studied. Alpha-band visual steady-state entrainment abnormalities in SZ are known to differ as a function of train duration (Clementz et al., 2004). Treatment with NMDA-receptor antagonists (a well-established pharmacological model of psychosis; Javitt et al., 2012) enhances 40-Hz aSSRs in humans and rats when long duration trains are employed (Plourde et al., 1997; Vohs et al., 2012) while reducing 40-Hz aSSRs when more traditional 500 ms trains are used (Sivarao et al., 2013). Thus a systematic investigation of SZ gamma-band aSSR abnormalities across different sensori-behavioral contexts is necessary for understanding the neurophysiological underpinnings of and effectively refining this promising marker of psychotic pathology. If SZ reductions in aSSR power are dependent on contextual variables, or are abnormally modulated by behaviorally relevant or sensory conditions, aSSRs may index an auditory-contextual processing abnormality beyond and/or in addition to basic gamma-synchrony deficits. This would have implications for how gamma-band aSSR deficits are interpreted, further refined, and utilized as a biomarker in future research.

Given what has been demonstrated regarding top-down attribution of attention to basic auditory discrimination (Javitt and Freedman, 2015; Javitt et al., 2012; Rabinowicz et al., 2000), we expected that attentional context (inclusion of an auditory discrimination task) would similarly affect SZ and healthy aSSRs. Given findings from Hamm et al. and Clementz et al., along with dependencies of SZ sensory cortical abnormalities on, for example, inter-stimulus interval (Rosburg et al., 2008) and temporal contextual processing (Light and Näätänen, 2013), we expected SZ aSSR abnormalities to be less modulated by temporal context of the presented stimulus trains (compared to H), reflecting potentially deficient sensory gain control and/or cortical adaption to dense, repetitive stimulation. The current study specifically addressed whether stimulus duration (500 ms vs 1500 ms) and attentional context (inclusion of an auditory discrimination task) of the recording block influenced SZ gamma-band auditory neural entrainment. Additionally, aSSR measurements were regressed on auditory discrimination performance to test the hypothesis that gamma-band synchrony and, specifically, the aSSR biomarker reflects auditory perceptual dysfunction in SZ.

2. Methods

2.1. Subjects

Eighteen persons with DSM-IV SZ (Mean \pm SD: 45.6 \pm 8.3 years, 9 females) and 18 healthy persons (40.8 \pm 9.9 years, 7 females) participated. SZ were recruited through community advertisements and through outpatient services of the Medical College of Georgia (Georgia Regents University, Augusta, GA); healthy subjects were recruited from the community. SZ were diagnosed using the Structured Clinical Interview for DSM-IV (First and Gibbon, 1997). The Positive and Negative Syndrome Scale (PANSS) quantified severity and extent of symptomatology (Kay et al., 1987 Table 1). All subjects were free of substance use disorders in the 6 months prior to testing. SZ were chronic patients with typical age of illness onsets. Medication information is provided in the Supplement. All participants provided informed consent and were paid for their time. This study was approved by the Institutional Review Boards at University of Georgia and Georgia Regents University.

2.2. Stimuli

Four blocks of 130–165 tones (carrier pitches 500-, 1000-, or 2000-Hz; randomly ordered) were presented binaurally through Etymotic insert earphones (Etymotic Research, Elk Grove Village, IL) at 76 dB SPL with an average 3 s ISI (range 2.7–3.3 s) while participants sat in a dark room with eyes open and fixated on a small cross presented on a computer monitor. Tones were either sinusoidally amplitude modulated (Krishnan et al., 2009) at 40-Hz (90%; “standards”) or unmodulated pure-tones (10%; “targets”). To the listener, “standards” resembled, for example, a phone ringing, while “targets” sounded like a smooth dial-tone. In 2 of the blocks, tones had a 500 ms duration (Kwon et al., 1999), while in the other 2 blocks each tone lasted 1500 ms (Hamm et al., 2012b). Further, in 2 of the blocks, participants were instructed to make a button press to “target” tones (“task” condition), while in the other 2 blocks participants were instructed to simply listen to the tones while fixating (“no-task” condition). Thus the 4 conditions were short-duration task, short-duration no-task, long-duration task, and long-duration no-task. Order of conditions was counter-balanced across subjects. Subjects’ comprehension and ability to perform the task was confirmed prior to data collection.

2.3. EEG recording

EEG data were recorded vertex-referenced using a 256 sensor Geodesic Sensor Net and NetAmps 200 amplifiers (Electrical Geodesics Inc.; EGI, Eugene, OR). Sensor impedances were kept below 50 k Ω , as is standard when using high input impedance amplifiers. Data were sampled at 500-Hz with an analog filter bandpass of 0.1–200-Hz.

Table 1

Participant information. H, healthy control subjects; SZ, schizophrenia subjects; CPZ, chlorpromazine; PANSS, Positive and Negative Syndrome Scale. (a) CPZ equivalents in mg. (b) symptom scores.

	H	SZ	Statistic	p-value
	39%	50%	$\chi^2[1] = 0.45$.502
<i>Female participants</i>				
Age (years)	41 (25–54)	46 (25–55)	$t(34) = 1.56$.126
Medication dosage ^a	–	207 (20–533)	–	–
PANSS positive ^b	–	13.7 (8–27)	–	–
PANSS negative ^b	–	14.8 (8–28)	–	–
PANSS general ^b	–	33.9 (17–64)	–	–
<i>Number of trials</i>				
Short no-task	117 (97–138)	111 (72–139)	$t(34) = 1.49$.145
Short task	120 (97–139)	111 (74–149)	$t(34) = 1.77$.090
Long no-task	94 (75–114)	87 (69–111)	$t(34) = 1.54$.131
Long task	94 (75–113)	94 (76–110)	$t(34) = -0.16$.878

2.4. Data screening

Sensors from the neck/face were excluded leaving 211 sensors for analysis. Raw data were inspected offline for bad sensors, which were interpolated (<5% for any participant) using a spherical spline interpolation method (BESA 5.0; MEGIS Software, Grafelfing, Germany). Data were then converted to an average reference montage and digitally bandpass filtered from 0.5 to 100-Hz (zero phase filter; rolloff: 6 and 48 dB/octave, respectively). A notch filter was applied at 60-Hz (2-Hz width) to eliminate line noise. Blink and cardiac artifacts were identified using Independent Components Analysis and removed (Delorme and Makeig, 2004). Because the aSSR was the primary measure of interest and because of the low signal-to-noise ratio for target evoked responses (~13 trials per condition), only EEG data from standard trials were analysed (Hamm et al., 2011). Data were segmented into single trial epochs beginning 750 ms before and ending 2250 ms after stimulus onset, and voltage values averaged from –100 to 0 ms were defined as the baseline and were subtracted from all timepoints on individual trials. Trials with activity >120 mV at any sensor were eliminated. One SZ subject and one H subject were dropped from the study due to excessive artifact, yielding 18 SZ and 18 H. The number of remaining standard trials did not differ between groups for any carrier frequency for any condition (all $p > .09$; Table 1).

2.5. Data analysis

Data from remaining standard trials (i.e. 40-Hz steady-state stimuli) were averaged for each subject within each condition and carrier pitch, yielding ERPs with 211 channels and 1500 timepoints. Because carrier pitch (500-, 1000-, 2000-Hz) did not systematically interact with aSSR topographies or SZ vs H differences for any condition (see Supplementary Methods and Figure S1), average ERPs were recalculated across all standard trials within a condition regardless of carrier pitch, resulting in 4 separate 211×1500 point ERPs per subject and enhancing the overall signal to noise ratio and, thus, the stability all evoked measurements (Picton et al., 2000).

Next, in order to use EEG data recorded from every sensor and, thus, to most accurately and comprehensively capture the spatial topography of evoked brain responses across time, spatial PCA (oblique rotation) was completed on 211-channel grand average waveforms concatenated across all 4 conditions (Carroll et al., 2008a; Hamm et al., 2012b, 2013) using Matlab (The Mathworks, Matick, MA). This resulted in two components (verified by a scree test) accounting for 79% and 14% of the overall spatial variance of the grand averaged evoked potentials (see Supplemental Methods for details). The dot product of each set of component weights with the spatial distribution of evoked potentials was

computed for each timepoint on each subject's grand average data, reducing the ERPs to one waveform per component for each subject for each condition. The resulting scores were analyzed instead of single sensors (i.e. as “virtual sensors”), minimizing the number of comparisons and maximizing the signal/noise ratio of the ERP data. From 500 ms pre- to 2000 ms post-stimulus onset, 500 ms windows centered on each sample of ERP for each virtual sensor were multiplied by a 250-sample Hanning window (500 ms). The window was shifted in one-sample (2 ms) steps and the squared absolute value of the Fast Fourier Transform (FFT; 2-Hz resolution) was calculated at each step (Brenner et al., 2009) yielding a time-frequency power plot ranging from –500 to 2000 ms and 0- to 55-Hz for each subject, component, and condition (Figs. 1 and S4). Power values were log transformed to ensure normality.

For statistical analysis of aSSRs, a mixed model ANOVA with DIAGNOSIS (H, SZ) as a between subjects factor and ATTENTION (no-task, task) and DURATION (500 ms, 1500 ms) as a within subject factors was carried out for 40-Hz power averaged within the first 500 ms after stimulus onset. A preliminary analysis established no differences in the pre-stimulus period (–500 ms to –250 ms to avoid overlap with post-stimulus-onset timepoints) for any frequency band, so pre-stimulus power was subtracted from post-stimulus-onset power for all analyses. Condition specific effect sizes between H and SZ were also calculated when interactions were present (Glass's Δ) and statistical significance was determined by bootstrapping 95% confidence intervals, recalculating 10,000 times after shuffling group membership (sampling with replacement).

For analyses of behavior (in the task conditions only), button presses happening between 100 ms after stimulus onset and 250 ms before the subsequent stimulus onset counted as responses. The difference between the z-transformations of the hit rate and the false alarm rate (d' or sensitivity index) and the average correct response latencies (RTs) were calculated (Macmillan and Creelman, 2005). A mixed model ANOVA with DIAGNOSIS (H, SZ) as a between subjects factor and DURATION (500 ms, 1500 ms) as a within subject factor was carried out for differences on d' and RTs for each stimulus duration condition. Correlations were calculated between each of these measures and aSSRs. The stability of r-values was assessed by bootstrapping 95% confidence intervals by recalculating r-values 10,000 times after resampling with replacement.

3. Results

While several main effects and interactions were present in PCA component 1, PCA component 2 did not yield significance main effects or interactions involving DIAGNOSIS. Thus results are only reported

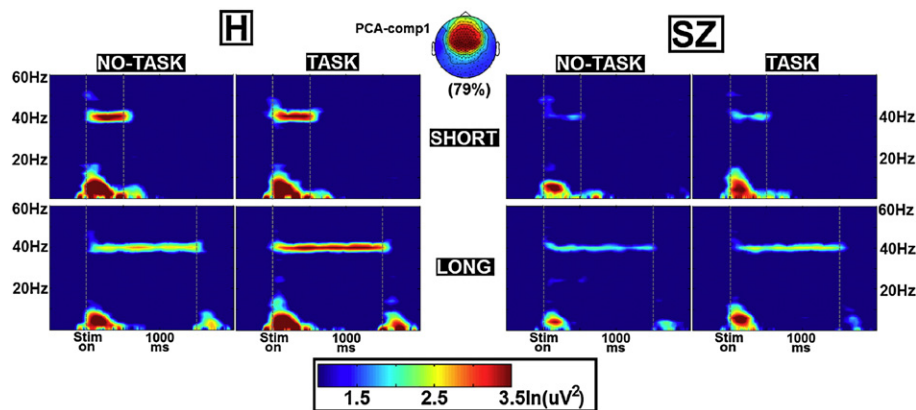


Fig. 1. Evoked power is plotted in heat maps as a function of time (x-axis) and frequency (y-axis) for each group and condition for spatial PCA component 1. Displayed in top-center (as a single topography) are the component weights of PCA component 1, which accounted for 79% of the total spatial variance of the grand-average evoked potentials across all conditions.

for PCA component 1 (Figs. 1–3). Group mean time-frequency spectra for PCA component 2 are available in Supplemental Figure S4.

3.1. 40-Hz auditory steady-state response

A DIAGNOSIS main effect ($F(1,34) = 9.24, p < .01$) and a DIAGNOSIS by DURATION interaction ($F(1,34) = 8.13, p < .01$) were present for aSSRs. While H showed a significant decrease of 40-Hz power for long compared to short duration stimulus trains ($t^{\text{paired}}(17) = 3.05, p^{\text{two-tailed}} < .01$; short mean = 3.44 [std = 1.1], long = 2.93 [1.3]; Fig. 2), SZ did not show a similar effect ($t^{\text{paired}}(17) = -1.72, p = .21$; short = 1.81 [1.2], long = 2.07 [1.1]). H vs SZ effect sizes for the short-duration conditions (Glass's $\Delta = 1.47, CI = [0.79, 2.13]$) and the long-duration conditions ($\Delta = 0.65, [0.05, 1.23]$) were both significantly different from each other and zero.

Consistent with the ambiguity of previous reports, the main effect of ATTENTION on aSSRs only approached significance ($F(1,34) = 3.35, p = .07$), hinting at a slight increase in entrainment power during the task (2.75 [1.6]) compared to the no-task condition (2.38 [1.1]). This effect was, however, equivalent between SZ and H as the ATTENTION by DIAGNOSIS interaction was not present ($F(1,34) = 0.94, p = .34$).

Overall, H, but not SZ, reduced gamma-band neural entrainment when long duration stimulus trains were presented. This resulted in larger H-SZ effect sizes for traditionally used 500 ms stimulus trains as compared to 1500 ms. Attentional context, or requiring a behavioral response to aSSR stimuli, does not impact SZ aSSR reductions.

3.2. Behavior

There was a significant effect of DIAGNOSIS on d-prime scores ($F(1,34) = 11.2, p < .01$), driven by SZ having significantly worse discrimination performance overall (mean = 4.56, [stdev = 2.57]) than H (6.82, [1.28]; $t(34) = 3.34, p < .01$). No main effects or interactions involving duration were present.

On response latency, a significant effect of DIAGNOSIS ($F(1,34) = 9.76, p < .01$) was driven by SZ showing slower responses overall (1210 ms[561]) than H (849 ms[415]; $t(34) = 3.12, p < .01$). Subjects displayed slower responses when provided with longer stimuli (925 ms[338] vs 1130 ms[492]; $t(17) = 4.18, p < .01$). No DIAGNOSIS by duration interaction was present.

Across all subjects, short duration aSSR power significantly correlated with both task performance (d-prime; $r = .47 [0.20, .74]; p < .01$) and response latency ($r = -.41, [-.66, -.12]; p < .05$; Fig. 3). When these analyses were limited to SZ or H groups, short aSSR correlations with d-prime retained the same direction and stability ($r^H = .18 [0.08, .83]; r^{SZ} = .37 [0.08, .83]$). Correlations of short aSSRs with response latency were relatively unstable when calculated within groups ($r^H = -.12 [-.76, .02]; r^{SZ} = -.31 [-.75, .02]$). Long duration aSSRs did not correlate with d-prime or latency.

4. Discussion

Gamma-band aSSR abnormalities in schizophrenia are moderated by the duration of the stimulus train, being less dramatic in contexts where short (500 ms) compared to long (1500 ms) trains are employed. In contrast, the presence of an ongoing auditory discrimination task, compared to passive listening, did not significantly affect SZ aSSR abnormalities. This pattern of findings provides key implications for the understanding of gamma-synchrony abnormalities in general, and for further refinement and use of gamma-band aSSRs as a biomarker for SZ.

The current results replicate the substantial SZ reductions in 40-Hz entrainment reported in 9 of 11 previous studies which used 500 ms stimulus trains (Gilmore et al., 2004; Hong et al., 2004; Kirihaara et al., 2012; Kwon et al., 1999; Light et al., 2006; Rass et al., 2012; Spencer et al., 2008; Teale et al., 2003, 2008; Tsuchimoto et al., 2011; Vierling-claassen et al., 2008a, 2008b). In blocks when longer (1500 ms) stimulus trains were presented in the current study, H reduced 40-Hz entrainment power relative to 500 ms blocks, but SZ did not. Because the cortico-cortical and thalamo-cortical circuitry underlying and modulating aSSR entrainment is not completely known, it remains unclear why a context of long duration stimulus trains (or more temporally dense stimulation contexts) results in an attenuated gamma-band response in H. One possibility is that this very adaptive response is absent in SZ and could relate to other auditory biomarkers in SZ such as P50 suppression (Hamm et al., 2012a) or mismatch negativity (Light and Näätänen, 2013) reflecting impaired short-term sensory memory processes resulting from NMDAR dysfunction on inhibitory interneurons (Gonzalez-Burgos and Lewis, 2012; Javitt et al., 1996; Lewis et al., 2012). This notion requires further study since an absence of short-stimulus facilitation is equally as likely as is failed long-stimulus adaptation to explain the current results.

This study demonstrates that the aSSR is reduced in SZ regardless of attentional investment, suggesting that aSSRs may index what has been referred to as a bottom-up sensory deficit in psychosis (Javitt, 2009) rather than a failed deployment of context-appropriate neuromodulation. Likewise, both H and SZ subjects who generated substantive 40-Hz auditory cortical entrainment to aSSR stimuli also differentiated such stimuli from unmodulated tones more quickly and more accurately in a perceptual task. This study indicates that reduced 40-Hz aSSRs in SZ may give rise to or reflect auditory perceptual dysfunction core to the disorder (Javitt and Freedman, 2015). This finding ascribes further functional disease relevance to aSSR as a biomarker. Interestingly, the association of entrainment power to behavior was only present in short stimulus contexts. A different perceptual strategy might be employed when longer, more information-abundant stimulation is available. Electrophysiological correlates of these strategies were not present in evoked responses recorded here, but the long-short distinction further echoes the idea that aSSR stimuli of different durations probe somewhat distinct cortical circuitry.

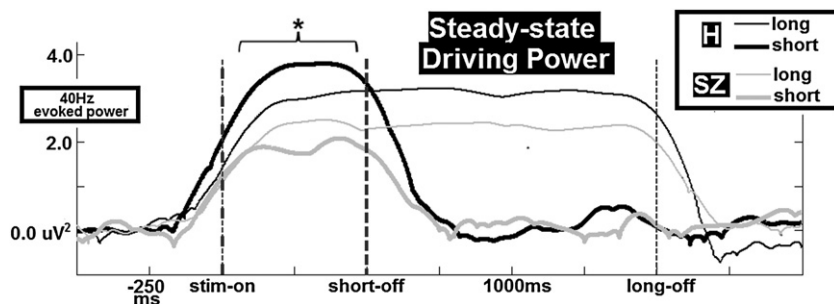


Fig. 2. 40-Hz power (aSSR, PCA-comp 1) is displayed for each group and duration condition. An asterisk (*) denotes a significant DIAGNOSIS by DURATION interaction effect for power in the first 500 ms after stimulus onset.

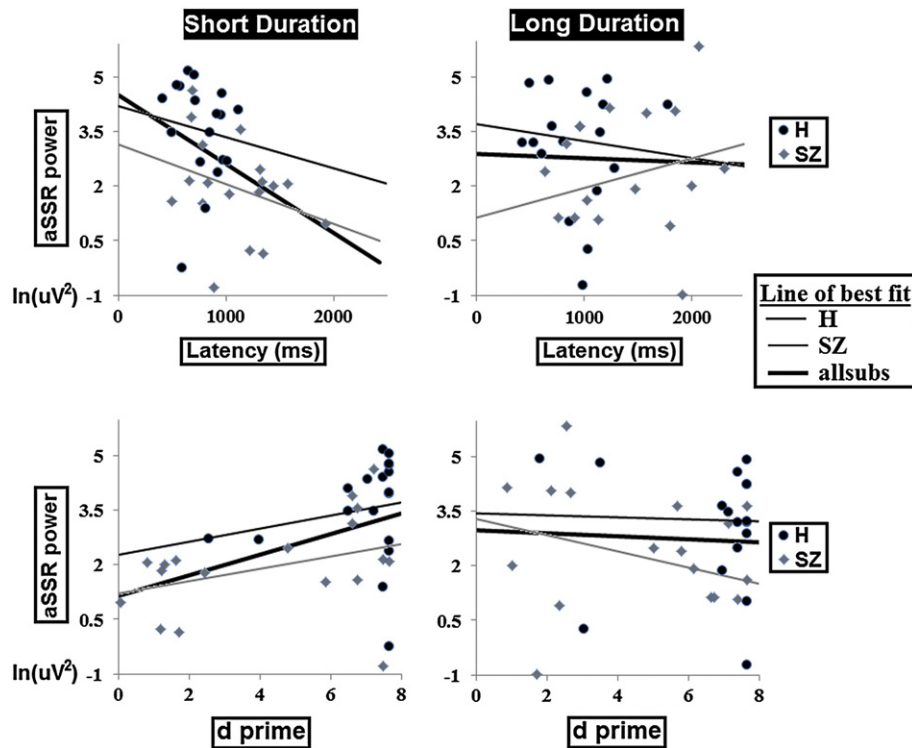


Fig. 3. Scatter plots of 40-Hz aSSR power (task condition only) plotted against response latency (above) and d-prime scores (below) reveal significant correlations for short duration (left) but not long duration contexts (right). Lines of best fit based on only H, on only SZ, and then on entire sample are overlaid for each plot.

Above all, many structural circuit motifs and neurotransmitter systems influence the generation of gamma-band oscillations. While the results of the current study advance the notion that stimulus train duration affects SZ aSSR entrainment abnormalities, they also indicate that duration, along with attentional context, cannot fully explain the SZ gamma-band augmentations shown in Hamm et al. (2012a, 2012b). Hamm et al. (2012b) also employed 1500 ms aSSR stimulus trains, but utilized more aurally dense broadband noise carriers (500–4000-Hz) instead of pure-tones. If bandwidth and/or temporal density (instantaneous clicks vs amplitude modulation) moderate SZ aSSR abnormalities, this finding might point at fundamental deviations in lateral inhibition mechanisms in cortical and/or subcortical auditory pathways. Consideration of nuanced context specific alterations like the effects presented herein and in future studies will be needed to mature the 40-Hz aSSR into a truly valuable disease biomarker. The fact that evoked low-frequency potentials (comparable to traditional ERPs) exhibited a more general reduction in SZ across duration contexts (similar to the dissociation shown in Hamm et al. (2012b); Fig. 1 and Supplementary Methods and Figure S5) suggest that gamma aSSRs show promise as a unique psychosis biomarker which should be mechanistically studied apart from basic sensory evoked responses.

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Contributors

JPH and BC designed the study. AEB, LKH, MEH, WTO, DAP, JEM, and PAB recruited, interviewed, and screened participants. JPH, AEB, LKH, MEH, WTO, and DAP collected data. JPH analysed data. All authors interpreted results. JPH wrote the manuscript. All authors edited the manuscript.

Conflict of interest

Mr. Hamm, Ms. Bobilev, Ms. Hayrynen, Mr. Hudgens-Haney, Mr. Oliver, Mr. Parker, Dr. McDowell, Dr. Buckley, and Dr. Clementz report no financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.schres.2015.02.016>.

References

- Baethge, C., Baldessarini, R.J., Freudenthal, K., Streuwitz, A., Bauer, M., Bschor, T., 2005. Hallucinations in bipolar disorder: characteristics and comparison to unipolar depression and schizophrenia. *Bipolar Disord.* 7, 136–145. <http://dx.doi.org/10.1111/j.1399-5618.2004.00175.x>.
- Basar-Eroglu, C., Brand, A., Hildebrandt, H., Karolina Kedzior, K., Mathes, B., Schmiedt, C., 2007. Working memory related gamma oscillations in schizophrenia patients. *Int. J. Psychophysiol.* 64, 39–45. <http://dx.doi.org/10.1016/j.ijpsycho.2006.07.007>.
- Brenner, C.A., Krishnan, G.P., Vohs, J.L., Ahn, W.-Y., Hetrick, W.P., Morzorati, S.L., O'Donnell, B.F., 2009. Steady state responses: electrophysiological assessment of sensory function in schizophrenia. *Schizophr. Bull.* 35, 1065–1077. <http://dx.doi.org/10.1093/schbul/sbp091>.
- Buzsaki, G., 2009. *Rhythms of the Brain*. Oxford University Press, New York.
- Carroll, C.A., Kieffaber, P.D., Vohs, J.L., O'Donnell, B.F., Shekhar, A., Hetrick, W.P., 2008a. Contributions of spectral frequency analyses to the study of P50 ERP amplitude and suppression in bipolar disorder with or without a history of psychosis. *Bipolar Disord.* 10, 776–787. <http://dx.doi.org/10.1111/j.1399-5618.2008.00622.x>.
- Carroll, C.A., Boggs, J., O'Donnell, B.F., Shekhar, A., Hetrick, W.P., 2008b. Temporal processing dysfunction in schizophrenia. *Brain Cogn.* 67, 150–161. <http://dx.doi.org/10.1016/j.bandc.2007.12.005>.
- Clementz, B.A., Blumenfeld, L.D., 2001. Multichannel electroencephalographic assessment of auditory evoked response suppression in schizophrenia. *Exp. Brain Res.* 139, 377–390.
- Clementz, B.A., Keil, A., Kissler, J., 2004. Aberrant brain dynamics in schizophrenia: delayed buildup and prolonged decay of the visual steady-state response. *Brain Res. Cogn. Brain Res.* 18, 121–129.
- Curley, A.A., Lewis, D.A., 2012. Cortical basket cell dysfunction in schizophrenia. *J. Physiol.* 590, 715–724. <http://dx.doi.org/10.1113/jphysiol.2011.224659>.
- Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* 134, 9–21. <http://dx.doi.org/10.1016/j.jneumeth.2003.10.009>.

- First, M.B., Gibbon, M., 1997. *User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version*. American Psychiatric Pub.
- Galambos, R., Makeig, S., Talmachoff, P.J., 1981. A 40-Hz auditory potential recorded from the human scalp. *Proc. Natl. Acad. Sci. U. S. A.* 78, 2643–2647.
- Gilmore, C.S., Ca, B.A.C., Buckley, P.F., 2004. Rate of stimulation affects schizophrenia-normal differences on the N1 auditory-evoked potential. *Schizophrenia* 15, 713–717.
- Gonzalez-Burgos, G., Lewis, D.A., 2008. GABA neurons and the mechanisms of network oscillations: implications for understanding cortical dysfunction in schizophrenia. *Schizophr. Bull.* 34, 944–961. <http://dx.doi.org/10.1093/schbul/sbn070>.
- Gonzalez-Burgos, G., Lewis, D.A., 2012. NMDA receptor hypofunction, parvalbumin-positive neurons, and cortical gamma oscillations in schizophrenia. *Schizophr. Bull.* 38, 950–957. <http://dx.doi.org/10.1093/schbul/sbs010>.
- Goodwin, D.W., Alderson, P., Rosenthal, R., 1971. Clinical significance of hallucinations in psychiatric disorders. A study of 116 hallucinatory patients. *Arch. Gen. Psychiatry* 24, 76–80.
- Griskova-Bulanova, I., Ruksenas, O., Dapsys, K., Maciulis, V., Arnfred, S.M.H., 2011. Distraction task rather than focal attention modulates gamma activity associated with auditory steady-state responses (ASSRs). *Clin. Neurophysiol.* 122, 1541–1548. <http://dx.doi.org/10.1016/j.clinph.2011.02.005>.
- Hall, M.-H., Taylor, G., Salisbury, D.F., Levy, D.L., 2010. Sensory gating event-related potentials and oscillations in schizophrenia patients and their unaffected relatives. *Schizophr. Bull.* 1–13. <http://dx.doi.org/10.1093/schbul/sbq027>.
- Hamm, J.P., Gilmore, C.S., Picchetti, N.A.M., Sponheim, S.R., Clementz, B.A., 2011. Abnormalities of neuronal oscillations and temporal integration to low- and high-frequency auditory stimulation in schizophrenia. *Biol. Psychiatry* 69, 989–996. <http://dx.doi.org/10.1016/j.biopsych.2010.11.021>.
- Hamm, J.P., Ethridge, L.E., Shapiro, J.R., Stevens, M.C., Boutros, N.N., Summerfelt, A.T., Keshavan, M.S., Sweeney, J.A., Pearson, G., Tamminga, C.A., Thaker, G., Clementz, B.A., 2012a. Spatiotemporal and frequency domain analysis of auditory paired stimuli processing in schizophrenia and bipolar disorder with psychosis. *Psychophysiology* 49, 522–530. <http://dx.doi.org/10.1111/j.1469-8986.2011.01327.x>.
- Hamm, J.P., Gilmore, C.S., Clementz, B.A., 2012b. Augmented gamma band auditory steady-state responses: support for NMDA hypofunction in schizophrenia. *Schizophr. Res.* 138, 1–7. <http://dx.doi.org/10.1016/j.schres.2012.04.003>.
- Hamm, J.P., Ethridge, L.E., Shapiro, J.R., Pearson, G.D., Tamminga, C.A., Sweeney, J.A., Keshavan, M.S., Thaker, G.K., Clementz, B.A., 2013. Family history of psychosis moderates early auditory cortical response abnormalities in non-psychotic bipolar disorder. *Bipolar Disord.* <http://dx.doi.org/10.1111/bdi.12110>.
- Hirano, Y., Oribe, N., Kanba, S., Onitsuka, T., Nestor, P.G., Spencer, K.M., 2015. Spontaneous gamma activity in schizophrenia. *JAMA Psychiatry*. <http://dx.doi.org/10.1001/jamapsychiatry.2014.2642>.
- Hong, L.E., Summerfelt, A., McMahon, R., Adami, H., Francis, G., Elliott, A., Buchanan, R.W., Thaker, G.K., 2004. Evoked gamma band synchronization and the liability for schizophrenia. *Schizophr. Res.* 70, 293–302. <http://dx.doi.org/10.1016/j.schres.2003.12.011>.
- Javitt, D.C., 2009. When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. *Annu. Rev. Clin. Psychol.* 5, 249–275. <http://dx.doi.org/10.1146/annurev.clinpsy.032408.153502>.
- Javitt, D.C., Freedman, R., 2015. Sensory processing dysfunction in the personal experience and neuronal machinery of schizophrenia. *Am. J. Psychiatry* 172, 17–31. <http://dx.doi.org/10.1176/appi.ajp.2014.13121691>.
- Javitt, D.C., Steinschneider, M., Schroeder, C.E., Arezzo, J.C., 1996. Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. *Proc. Natl. Acad. Sci. U. S. A.* 93, 11962–11967.
- Javitt, D.C., Zukin, S.R., Heresco-Levy, U., Umbricht, D., 2012. Has an angel shown the way? Etiological and therapeutic implications of the PCP/NMDA model of schizophrenia. *Schizophr. Bull.* 38, 958–966. <http://dx.doi.org/10.1093/schbul/sbs069>.
- Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13, 261–276.
- Kirihara, K., Rissling, A.J., Swerdlow, N.R., Braff, D.L., Light, G.A., 2012. Hierarchical organization of gamma and theta oscillatory dynamics in schizophrenia. *Biol. Psychiatry* 71, 873–880. <http://dx.doi.org/10.1016/j.biopsych.2012.01.016>.
- Krishnan, G.P., Hetrick, W.P., Brenner, C.A., Shekhar, A., Steffen, A.N., O'Donnell, B.F., 2009. Steady state and induced auditory gamma deficits in schizophrenia. *Neuroimage* 47, 1711–1719.
- Kwon, J.S., O'Donnell, B.F., Wallenstein, G.V., Greene, R.W., Hirayasu, Y., Nestor, P.G., Hasselmo, M.E., Potts, G.F., Shenton, M.E., McCarley, R.W., 1999. Gamma frequency-range abnormalities to auditory stimulation in schizophrenia. *Arch. Gen. Psychiatry* 56, 1001–1005.
- Lewis, D.A., Curley, A.A., Glausier, J.R., Volk, D.W., 2012. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. *Trends Neurosci.* 35, 57–67. <http://dx.doi.org/10.1016/j.tins.2011.10.004>.
- Light, G.A., Näätänen, R., 2013. Mismatch negativity is a breakthrough biomarker for understanding and treating psychotic disorders. *Proc. Natl. Acad. Sci. U. S. A.* 110, 15175–15176. <http://dx.doi.org/10.1073/pnas.1313287110>.
- Light, G.A., Hsu, J.L., Hsieh, M.H., Meyer-Gomes, K., Sprock, J., Swerdlow, N.R., Braff, D.L., 2006. Gamma band oscillations reveal neural network cortical coherence dysfunction in schizophrenia patients. *Biol. Psychiatry* 60, 1231–1240. <http://dx.doi.org/10.1016/j.biopsych.2006.03.055>.
- Macmillan, N., Creelman, C., 2005. *Detection Theory: A User's Guide*. Lawrence Erlbaum Associates, Mahwah, New Jersey.
- Moran, L.V., Hong, L.E., 2011. High vs low frequency neural oscillations in schizophrenia. *Schizophr. Bull.* 37, 659–663. <http://dx.doi.org/10.1093/schbul/sbr056>.
- Oda, Y., Onitsuka, T., Tsuchimoto, R., Hirano, S., Oribe, N., Ueno, T., Hirano, Y., Nakamura, I., Miura, T., Kanba, S., 2012. Gamma band neural synchronization deficits for auditory steady state responses in bipolar disorder patients. *PLoS One* 7, e39955. <http://dx.doi.org/10.1371/journal.pone.0039955>.
- Picton, T.W., Bentin, S., Berg, P., Donchin, E., Hillyard, S.A., Johnson, R., Miller, G.A., Ritter, W., Ruchkin, D.S., Rugg, M.D., Taylor, M.J., 2000. Guidelines for using human event-related potentials to study cognition: recording standards and publication criteria. *Psychophysiology* 37, 127–152.
- Picton, T.W., John, M.S., Dimitrijevic, A., Purcell, D., 2003. Human auditory steady-state responses. *Int. J. Audiol.* 42, 177–219.
- Plourde, G., Baribeau, J., Bonhomme, V., 1997. Ketamine increases the amplitude of the 40-Hz auditory steady-state response in humans. *Br. J. Anaesth.* 78, 524–529.
- Rabinowicz, E.F., Silipo, G., Goldman, R., Javitt, D.C., 2000. Auditory sensory dysfunction in schizophrenia: imprecision or distractibility? *Arch. Gen. Psychiatry* 57, 1149–1155.
- Rass, O., Forsyth, J.K., Krishnan, G.P., Hetrick, W.P., Klaunig, M.J., Breier, A., O'Donnell, B.F., Brenner, C. a., 2012. Auditory steady state response in the schizophrenia, first-degree relatives, and schizotypal personality disorder. *Schizophr. Res.* 136, 143–149. <http://dx.doi.org/10.1016/j.schres.2012.01.003>.
- Rosburg, T., Boutros, N.N., Ford, J.M., 2008. Reduced auditory evoked potential component N100 in schizophrenia—a critical review. *Psychiatry Res.* 161, 259–274. <http://dx.doi.org/10.1016/j.psychres.2008.03.017>.
- Ross, B., Picton, T.W., Herdman, A.T., Pantev, C., 2004. The effect of attention on the auditory steady-state response. *Neurol. Clin. Neurophysiol.* 2004, 22.
- Saupe, K., Widmann, A., Bendixen, A., Müller, M.M., Schröger, E., 2009. Effects of intermodal attention on the auditory steady-state response and the event-related potential. *Psychophysiology* 46, 321–327. <http://dx.doi.org/10.1111/j.1469-8986.2008.00765.x>.
- Sivara, D.V., Frenkel, M., Chen, P., Healy, F.L., Lodge, N.J., Zaczek, R., 2013. MK-801 disrupts and nicotine augments 40 Hz auditory steady state responses in the auditory cortex of the urethane-anesthetized rat. *Neuropharmacology* 73C, 1–9. <http://dx.doi.org/10.1016/j.neuropharm.2013.05.006>.
- Spencer, K.M., Nestor, P.G., Perlmuter, R., Niznikiewicz, M.A., Klump, M.C., Frumin, M., Shenton, M.E., McCarley, R.W., 2004. Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proc. Natl. Acad. Sci. U. S. A.* 101, 17288–17293. <http://dx.doi.org/10.1073/pnas.0406074101>.
- Spencer, K.M., Salisbury, D.F., Shenton, M.E., McCarley, R.W., 2008. Gamma-band auditory steady-state responses are impaired in first episode psychosis. *Biol. Psychiatry* 64, 369–375. <http://dx.doi.org/10.1016/j.biopsych.2008.02.021>.
- Teale, P., Carlson, J., Rojas, D., Reite, M., 2003. Reduced laterality of the source locations for generators of the auditory steady-state field in schizophrenia. *Biol. Psychiatry* 54, 1149–1153. [http://dx.doi.org/10.1016/S0006-3223\(03\)00411-6](http://dx.doi.org/10.1016/S0006-3223(03)00411-6).
- Teale, P., Collins, D., Maharaj, K., Rojas, D.C., Kronberg, E., Reite, M., 2008. Cortical source estimates of gamma band amplitude and phase are different in schizophrenia. *Neuroimage* 42, 1481–1489. <http://dx.doi.org/10.1016/j.neuroimage.2008.06.020>.
- Traub, R.D., Bibbig, A., LeBeau, F.E.N., Buhl, E.H., Whittington, M.A., 2004. Cellular mechanisms of neuronal population oscillations in the hippocampus in vitro. *Annu. Rev. Neurosci.* 27, 247–278. <http://dx.doi.org/10.1146/annurev.neuro.27.070203.144303>.
- Tsuchimoto, R., Kanba, S., Hirano, S., Oribe, N., Ueno, T., Hirano, Y., Nakamura, I., Oda, Y., Miura, T., Onitsuka, T., 2011. Reduced high and low frequency gamma synchronization in patients with chronic schizophrenia. *Schizophr. Res.* <http://dx.doi.org/10.1016/j.schres.2011.07.020>.
- Uhlhaas, P.J., Singer, W., 2010. Abnormal neural oscillations and synchrony in schizophrenia. *Nat. Rev. Neurosci.* 11, 100–113. <http://dx.doi.org/10.1038/nrn2774>.
- Uhlhaas, P.J., Linden, D.E.J., Singer, W., Haenschel, C., Lindner, M., Maurer, K., Rodriguez, E., 2006. Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *J. Neurosci.* 26, 8168–8175. <http://dx.doi.org/10.1523/JNEUROSCI.2002-06.2006>.
- Vierling-claassen, D., Siekmeier, P., Stufflebeam, S., Kopell, N., 2008a. Modeling GABA Alterations in Schizophrenia: A Link Between Impaired Inhibition and Altered Gamma and Beta Range Auditory Entrainment. pp. 2656–2671. <http://dx.doi.org/10.1152/jn.00870.2007>.
- Vierling-claassen, D., Siekmeier, P., Stufflebeam, S., Kopell, N., 2008b. Modeling GABA alterations in schizophrenia: a link between impaired inhibition and altered gamma and beta range auditory entrainment. *J. Neurophysiol.* 99, 2656–2671. <http://dx.doi.org/10.1152/jn.00870.2007>.
- Vohs, J.L., Chambers, R.A., O'Donnell, B.F., Krishnan, G.P., Morzorati, S.L., 2012. Auditory steady state responses in a schizophrenia rat model probed by excitatory/inhibitory receptor manipulation. *Int. J. Psychophysiol.* 86, 136–142. <http://dx.doi.org/10.1016/j.jpsycho.2012.04.002>.