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# Delta Vs Gamma Auditory Steady State Synchrony in Schizophrenia

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***Background:*** **Delta band (1–4 Hz) neuronal responses support the precision and stability of auditory processing, and a deficit in delta band synchrony may be relevant to auditory domain symptoms in schizophrenia patients.** ***Methods:*** **Delta band synchronization elicited by a 2.5 Hz auditory steady state response (ASSR) paradigm, along with those from theta (5 Hz), alpha (10 Hz), beta (20 Hz), gamma (40 Hz), and high gamma (80 Hz) frequency ASSR, were compared in 128 patients with schizophrenia, 108 healthy controls, and 55 first-degree relatives (FDR) of patients.** ***Results:*** **Delta band synchronization was significantly impaired in patients compared with controls ($F = 18.3$, $P < .001$). There was a significant 2.5 Hz by 40 Hz ASSR interaction ($P = .023$), arising from a greater reduction of 2.5 Hz ASSR than of 40 Hz ASSR, in patients compared with controls. Greater deficit in delta ASSR was associated with auditory perceptual abnormality ($P = .007$) and reduced verbal working memory ($P < .001$). Gamma frequency ASSR impairment was also significant but more modest ($F = 8.7$, $P = .004$), and this deficit was also present in FDR ($P = .022$).** ***Conclusions:*** **The ability to sustain delta band oscillation entrainment in the auditory pathway is significantly reduced in schizophrenia patients and appears to be clinically relevant.**

*Key words:* auditory/hallucination/working memory/schizophrenia/auditory steady state/delta/gamma/ASSR

## Introduction

Many schizophrenia-related symptoms, such as auditory hallucination, speech disorganization, disorganized thoughts, and verbal working memory (VWM) deficits are in the auditory–verbal domain, suggesting that the schizophrenia disease process impacts the auditory processing pathway. Electrophysiological abnormalities in schizophrenia are consistently reported in patients during auditory paradigms such as auditory mismatch negativity,[1,2] steady-state response,[3,4] sensory gating,[5,6] and word, language and speech processing.[7,8] Auditory–verbal processing deficits in schizophrenia may thus be associated with fundamental electrophysiological deficits in the auditory processing network.

Cortical oscillations are thought to play an important role in cognitive functioning, communication, and integration of information across different regions of the brain.[9–11] In healthy subjects, low frequency oscillations (<10 Hz) regulate speech processing,[12] where accurate perception of attended speech is associated with more precise delta band (1–4 Hz) neuronal responses[13,14] than in other bands. These low frequency oscillations, especially in the delta band, appear to serve a stabilization and enhancement function while attending to, and during the processing of, auditory streams.[15] Auditory selective attention is also associated with the entrainment of ongoing neuronal oscillations in the delta band, which modulates neuronal excitability in primary auditory cortex.[16] We hypothesized that in schizophrenia a reduced ability to generate synchronous delta oscillations in response to auditory stimuli would disrupt auditory processing, leading to auditory–verbal domain problems.

The auditory steady-state response (ASSR) can be used to test the integrity of cortical oscillatory activity.[17–19] It is a robust activation paradigm to elicit frequency-specific auditory responses. It is generated using stimuli that are repeated (periodic) at a specified frequency, resulting in electroencephalographic neural entrainment at the presentation frequency. We used a 2.5 Hz (mean of 1–4 Hz) stimulus train to elicit ASSR in the delta band, and to test the joint hypotheses that (1) schizophrenia is associated with an inability to support delta synchronization,

and (2) this impairment is associated with cognitive disturbances and other symptoms in the auditory–verbal domain.

Our study is the first to investigate the delta (1–4 Hz) range ASSR in schizophrenia. Previous studies using attention-based paradigms have shown that delta entrainment is associated with clinical symptoms in schizophrenia.[20] ASSR has appeal in translational research for studying intrinsic neurobiological abnormalities without the need to rely on explicit behavioral performance. The first study to investigate ASSR in the 20–40 Hz range in schizophrenia reported reduced ASSR at 40 Hz.[3] Subsequent ASSR studies expanded the range down to 5–10 Hz or up to 80–160 Hz,[21,22] and have generally confirmed ASSR deficits in schizophrenia[4,21–28] primarily in the 40–80 Hz range. The strong interest in 40 Hz has also been justified by finding a reduced 40 Hz ASSR in the first-degree relatives (FDR) of schizophrenia patients.[27,29] FDR typically have about a 10-fold increase in risk for schizophrenia compared with the general population, although risks do not necessitate a transition to psychosis as the rate of schizophrenia is about 10% in FDR.[30,31] Given these findings, we investigated delta band ASSR, along with higher frequencies at 5, 10, 20, 40, and 80 Hz, with a focus on assessing the relationship between delta (2.5 Hz) vs gamma (40–80 Hz). This design also allowed an unbiased assessment across a very broad range of frequencies, to determine whether there may be frequency specificity in schizophrenia psychopathology.

## Methods

### *Participants*

The study included 128 schizophrenia spectrum disorder (SSD) patients and 108 healthy controls (HC) (table 1). The Structured Clinical Interview for DSM was used to make Axis I diagnoses. All patients were recruited from outpatient clinics; media advertisements were used for HC. Subjects with medical and neurological illnesses, head injury, and substance dependence or abuse (except nicotine) were excluded. Six patients were not on antipsychotics, 19 on typical, 74 on one atypical, 18 on more than one atypical, and 11 on a combination of atypical and typical antipsychotics. Patients on daily GABAergic hypnotics were excluded. Significant findings in SSD were re-examined in FDR of patients ($n = 55$) who have no psychosis. Seventy percentage of the FDR were from families of the patients in this study. All patient probands of the FDR were interviewed by SCID regardless of whether the patients were in the current study.

### *Auditory Clinical and Cognitive Symptoms*

We developed the Auditory Perceptual Trait and State Scale (APTS) to measure perceptual abnormalities. The anomalies are rated for "trait," defined as longitudinally experienced symptoms over one's lifetime, and "state," defined as symptoms recently experienced in the past week. The full scale is available at http://www.mdbrain.org/APTS.pdf. The APTS is self-rated. Its test–retest reliability was assessed in 41 participants about 4 months apart, which showed ICC = 0.81 for both the trait and state measures, suggesting good reliability. The Brief Psychiatric Rating Scale (BPRS) was used to rate overall symptoms. The APTS was administered to all participants; the BPRS only to patients. Finally, auditory– VWM was assessed using the digit sequencing task.[27,29]

### *ASSR Paradigm*

ASSRs were recorded in a sound-attenuated chamber while participants listened to click trains, delivered by headphones, at 2.5, 5, 10, 20, 40, and 80 Hz. Seventy-five stimulus trains (trials) each consisting of 15 clicks, with each click at 72 dB and of 1 ms duration were delivered at each stimulus frequency. The duration ranged from 6 s per train for 2.5 Hz, to 0.1875 s per train for 80 Hz. The inter-train interval was 0.7 s. Therefore, the durations for 2.5, 5, 10, 20, 40, and 80 Hz were 8.38, 4.69, 2.82, 1.89, 1.42, and 1.19 min, respectively, presented in 6 separate blocks separated by 2 min. The order of the blocks was randomized. This design allows steady-state

**Table 1.** Demographic and Clinical Information

| | | | | HC Vs SSD | | HC Vs FDR | |
|---|---|---|---|---|---|---|---|
| | HC ($n = 108$) | SSD ($n = 128$) | FDR ($n = 55$) | $F$ or $\chi^2$ | $P$ Value | $F$ or $\chi^2$ | $P$ Value |
| Age mean (SD) | 37.9 (13.8) | 37.8 (13.1) | 46.6 (13.6) | 0.003 | .96 | 15.1 | <.001** |
| % Male | 65.7 | 67.2 | 31.6 | 0.06 | .89 | 17.5 | <.001** |
| Verbal working memory | 20.4 (4.4) | 17.0 (5.3) | 18.9 (5.1) | 24.8 | <.001** | 3.4 | .067 |
| Auditory perception trait | 3.8 (4.8) | 19.4 (11.8) | 4.8 (7.7) | 140.3 | <.001** | 0.9 | .35 |
| Auditory perception state | 1.1 (2.4) | 9.8 (12.0) | 3.8 (4.8) | 46.4 | <.001** | 0.5 | .46 |
| BPRS | n/a | 40.4 (11.2) | n/a | n/a | n/a | n/a | n/a |

*Note*: BPRS, Brief Psychiatric Rating Scale; HC, healthy controls; SSD, schizophrenia spectrum disorder patients; FDR, first-degree relatives of SSD patients.
**Statistically significant.

neural entrainment for each frequency (figure 2 and supplementary figure S1). A hearing screening test excluded apparent hearing impairment. EEG was recorded using a 64 electrode Quick-Cap with sintered Ag/Ag chloride electrodes and a Neuroscan SynAmp[2] (Compumedics, Charlotte, NC) at 1000 Hz with a 0.1–200 Hz bandpass filter. Impedance was kept below 5 kΩ. Offline, electrodes were average referenced, high-pass filtered at 0.8 Hz, and detrended. Ocular artifacts were removed using the time-shift-PCA algorithm, with ocular channels as references.[32] The full-duration waveforms from each channel were epoched into 75 individual trials.

### *Normalized ASSR Power*

While typical ASSR analysis uses individual channels (often CZ or FZ), we adapted signal processing techniques[33,34] where individual EEG channels are spatially combined to maximize response reliability using the denoising source separation (DSS) algorithm.[35–37] DSS is a blind source separation technique related to principal component analysis (PCA) and independent component analysis (ICA) but specifically designed for use with data from multi-trial evoked responses or narrowband signals. DSS works by enhancing stimulus-driven activity over stimulus-unrelated activity, with its components ordered according to their reliability[35–37] [details in supplementary information].

Raw ASSR power was calculated as the magnitude squared of the Fourier transform at the stimulus frequency. The Fourier transform was calculated using concatenated trials rather than averaged trials to increase spectral resolution.[38,39] Background power was calculated as average spectral power over 1 Hz width frequency bands (on either side of the stimulus frequency, after leaving a guard band of 0.5 Hz on either side). Normalized ASSR power was then calculated as the mean over DSS components of the ratio of raw ASSR power and respective background power. This normalization with respect to background power dramatically reduces subject-to-subject variability of frequency response profiles.[38] This combined use of DSS and normalized ASSR power represents the 2 critical improvements over previous ASSR power extraction methods. The accompanying reduction of noise is particularly critical for low frequency ASSR, which is known to be more susceptible to background low frequency fluctuations.[17,33]

### *ASSR Phase Locking Value*

Phase locking value (PLV)[40] has been extensively used in ASSR analysis. Increased variability of neural responses across trials reduces the PLV value toward 0, whereas increased reliability increases the value toward 1.[41] First, intra-electrode PLV was calculated for each stimulus frequency at each electrode (algorithm in SI). Based on topographic analysis showing that ASSR was strongest at fronto-central locations (figure 1), the PLV of 16 fronto-central electrodes (AF3, AFZ, AF4, F3, F1, FZ, F2, F4, FC3, FC1, FCZ, FC2, FC4, C1, CZ, C2) were averaged and used for the final PLV assessment.

### *Statistics*

Data processing was performed without the knowledge of group and demographic information. Repeated measures ANOVA was performed to compare normalized ASSR power by stimulus frequency (6) and group (SSD vs HC). The Greenhouse-Geisser correction was applied. Significant effect was followed by post hoc comparison using Bonferroni correction ($P < .008$). If a significant difference was found for SSD vs HC, we then further

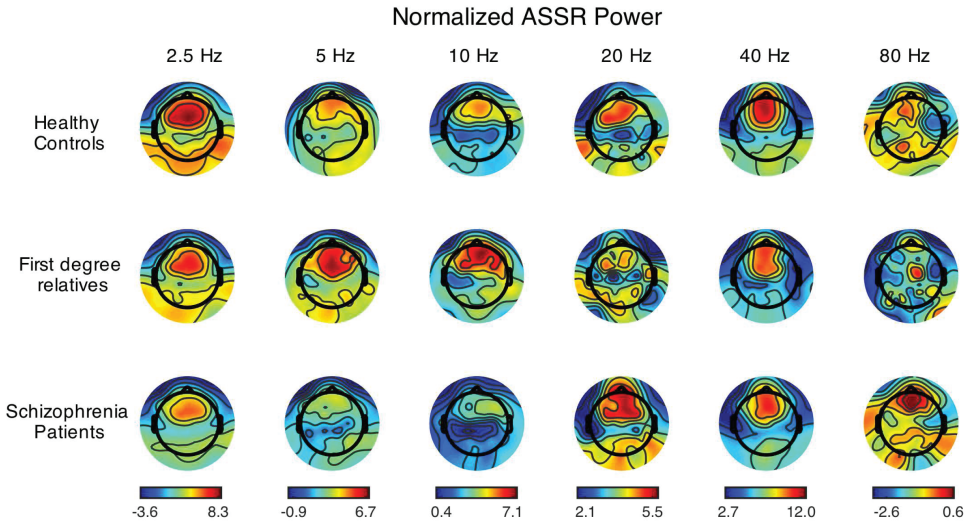


**Fig. 1.** Grand averages of topographies of normalized ASSR power for healthy controls, first-degree relatives, and schizophrenia spectrum disorder patients. Scaled based on lowest (blue) to highest power value (red) within each frequency. Refer to Results for statistical group differences.

tested whether the same frequency was significantly different between FDR vs HC (no further Bonferroni correction was applied). A similar analysis was followed for the PLV measure. Contributions of ASSR to clinical measures were examined using stepwise linear regression, where at each step the ASSR power at the 6 frequencies were the predictors and one clinical measure was the dependent variable. Multi-collinearity was examined using variance inflation factor (VIF).[42] A regression model was considered significant if the overall model was significant at $P < .05$ and all predictors had VIF <5. All tests were 2-tailed.

## Results

### *ASSR in SSD Patients*

Figure 1 shows that the spatial distribution of normalized ASSR power has a fronto-central accentuation; figure 2 shows grand average time courses of the ASSR responses from electrode FZ. Repeated measures ANOVA on normalized ASSR power extracted by DSS showed significant effects for stimulus frequency ($F = 390.1$, $P < .001$), group (SSD vs HC; $F = 13.4$, $P < .001$) and a frequency × group interaction ($P = .039$). Post hoc tests showed that the SSD group had significantly reduced power at 2.5 Hz

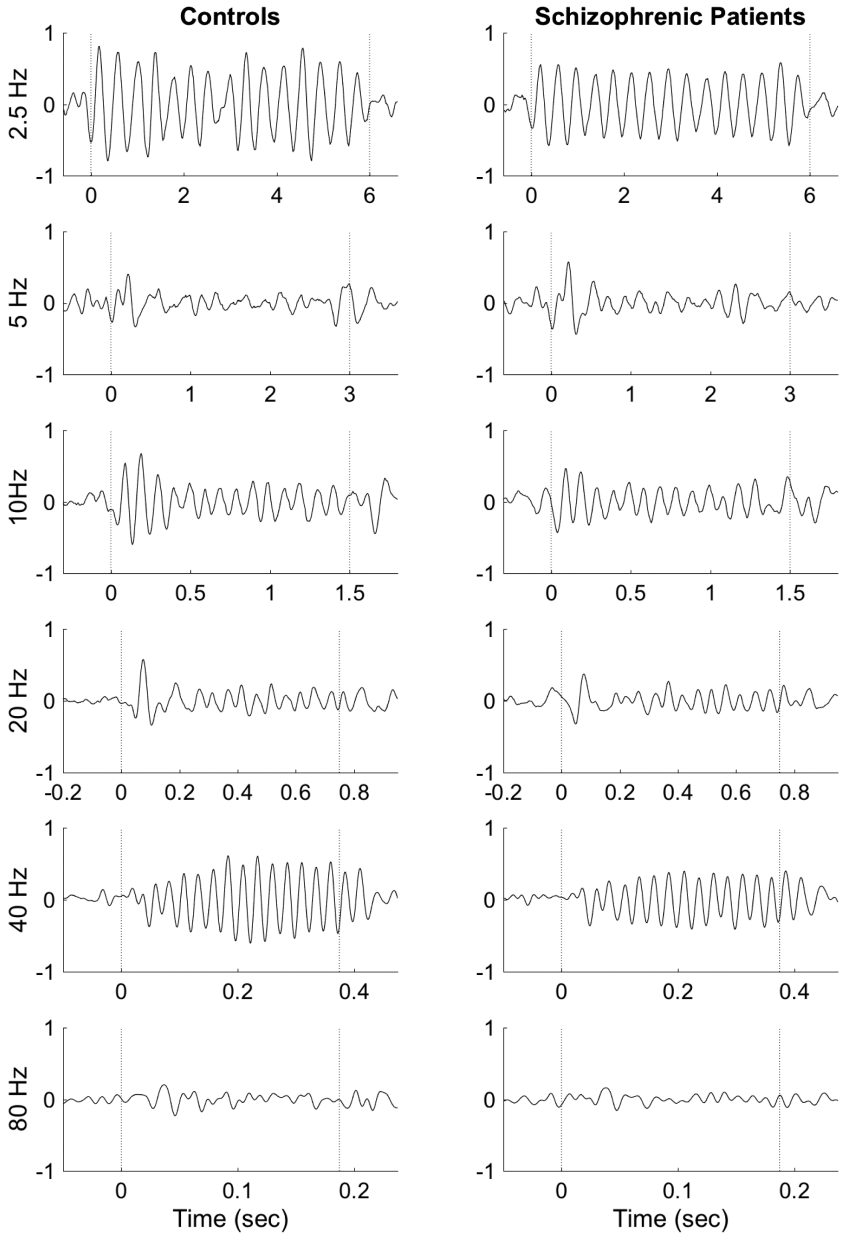


**Fig. 2.** Time-domain grand averages from electrode FZ. The vertical axis shows amplitude in μV. The vertical dotted lines indicate begin and end points of a stimulus train. Preferential entrainment in the delta (2.5 Hz) and gamma (40 Hz) bands can be seen in both the controls and schizophrenic patient group, and 2.5 Hz and 40 Hz stimuli are also associated with larger patient–control differences.

($F$ = 18.3, $P$ < .001), 5 Hz ($F$ = 10.1, $P$ = .002), 10 Hz ($F$ = 9.9, $P$ = .002), and 40 Hz ($F$ = 8.7, $P$ = .004), but not 20 Hz ($P$ = .18) or 80 Hz ($P$ = .03) after Bonferroni correction (figure 3A). When the analogous analysis was performed on ASSR responses without the use of DSS (eg, from the single electrode FZ) and without normalization, most findings of significance were lost: only 40 Hz ASSR showed nominally significant reduction in SSD compared with HC ($P$ = .017), which was then lost after correcting for multiple comparisons (supplementary figure S2B).

To formally test the frequency × group interaction between 2.5 and 40 Hz, ANOVA was repeated contrasting these frequencies. It showed significant group ($P$ < .001) and interaction effects ($P$ = .023), where the interaction was due to a greater reduction of 2.5 Hz ASSR than of 40 Hz ASSR, in patients compared with controls, as seen in figure 3A.

Re-examining these findings using PLV, significant effects were seen for frequency ($P$ < .001) and group ($P$ < .001) without interaction ($P$ = .09). Patients had reduced PLV at 2.5 Hz ($F$ = 9.5, $P$ = .002), 5 Hz ($F$ = 8.2, $P$ = .004), 10 Hz ($F$ = 5.9, $P$ = .016), 40 Hz ($F$ = 5.3, $P$ = .022) and 80 Hz ($F$ = 4.0, $P$ = .045) but not 20 Hz ($P$ = .50). Findings from 2.5, 5, 10, and 40 Hz replicated power-based analyses and thus no further Bonferroni correction was applied (figure 3B). Therefore, reduced ASSR was found in 2.5, 5, 10, and 40 Hz in both power and phase based analysis.

### *ASSR in FDR*

Age and sex were not matched between FDR and HC (table 1). However, neither age ($P$ = .44) nor sex ($P$ = .44) were significant in the repeated measures ANCOVA and so were removed. The results showed significant effects for stimulus frequency ($F$ = 171.0, $P$ < .001), group ($F$ = 5.1, $P$ = .025), and frequency × group interaction ($P$ = .036) in FDR vs HC. Post hoc tests at the frequencies for which SSD and HC were significantly different (2.5, 5, 10, and 40 Hz) showed that FDR had lower ASSR power than HC at 40 Hz ($F$ = 5.4, $P$ = .022) but not at 2.5, 5, or 10 Hz ($P$ = .28–.85) (figure 3C). Only the reduction in gamma band ASSR at 40 Hz was considered a replication of findings in patients.

For PLV, age ($P$ = .71) and sex ($P$ = .88) were not significant. There was a significant stimulus frequency effect ($F$ = 84.4, $P$ < .001) and a frequency × group interaction ($F$ = 3.5, $P$ = .007). Post hoc tests showed that only the 40 Hz ASSR reduction ($F$ = 5.5, $P$ = .021) was replicated (figure 3D).

In summary, findings were largely consistent between normalized power and PLV except with PLV generally having smaller effect sizes (figure 3; supplementary tables 1 and 2). In subsequent analyses, we opted to use only normalized power based ASSR.

### *ASSR and VWM*

Working memory is impaired in SSD.[43,44] While the SSD group had lower VWM compared with HC ($P$ < .001,

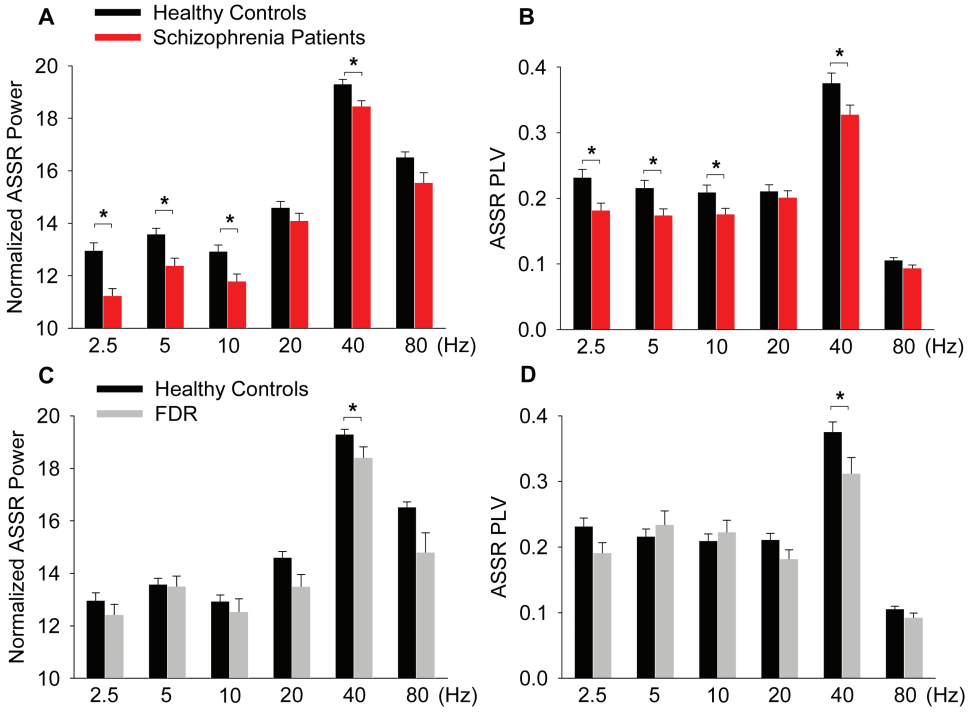


**Fig. 3.** Mean and SE of normalized power (in dB) and phase locking values (PLV). (A) Power at 2.5, 5, 10, and 40 Hz are significantly lower for patients than controls. (B) Replicable findings using PLV. (C and D) First-degree relatives showed replicable auditory steady state response reduction compared with controls only at 40 Hz. *Statistically significant. Effect sizes are tabulated in supplementary table 1.

table 1), the FDR did not significantly differ from HC on VWM ($P$ = .067). The regression model was significant in SSD ($F$ = 15.8, $\Delta R^2$ = 11.8%, $P$ < .001; all VIFs < 1.5) where only 2.5 Hz ASSR significantly contributed to VWM ($t$ = 4.0, $P$ < .001): patients with lower delta power showed worse VWM ($r$ = .36, $P$ < .001) (figure 4A). The correlation of 2.5 Hz ASSR with VWM was not significant in either the HC or FDR groups (supplementary figure S3).

We calculated the correlation coefficients between VWM and ASSR at each frequency: 2.5 Hz: $r$ = .34, $P$ < .001; 5 Hz: $r$ = .30, $P$ = .001; 10 Hz: $r$ = .22, $P$ = .016; 20 Hz: $r$ = .19, $P$ = .040; 40 Hz: $r$ = .20, $P$ = .033; and 80 Hz: $r$ = .15, $P$ = .11. The relationship between ASSR and VWM, quantified through these correlation coefficients, was strongly linked to the stimulus frequency ($r$ = −.95, $P$ = .003) (figure 4C): the correlation between ASSR and VWM significantly decreases with increasing stimulus frequency.

The model was also significant in FDR ($F$ = 9.8, $\Delta R^2$ = 17.5%, $P$ = .003; VIFs < 3.6) where only the 40 Hz ASSR significantly contributed to VWM ($t$ = 3.13, $P$ = .003) (figure 4B). The model was not significant in controls (model $P$ > .05).

### *ASSR and Auditory Perception Abnormality*

A regression model with APTS trait score as the dependent variable and normalized ASSR power as predictors in the SSD group was significant ($F$ = 7.7, $\Delta R^2$=13.8%, $P$ = .001; VIFs < 1.5). Only 2.5 Hz ($t$ = −2.8, $\Delta R^2$ = 6.8%, $P$ = .007) and 40 Hz ($t$ = 3.6, $\Delta R^2$ = 6.9%, $P$ = .001) normalized ASSR powers were significant predictors but in opposite directions: reduced 2.5 Hz and increased 40 Hz ASSR were associated with more longitudinally experienced auditory symptoms in SSD patients (figures 5B and 5C). The model was not significant for state auditory symptoms ($P$ = .056) although the trends were the same.

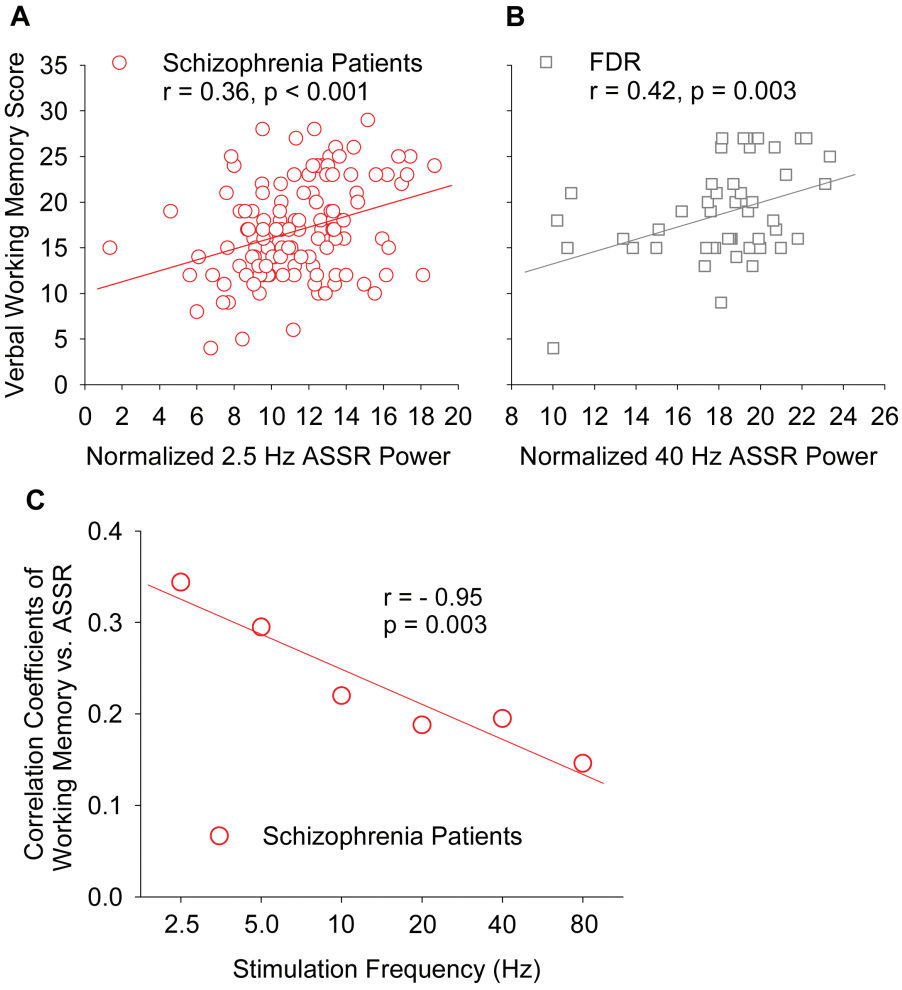


**Fig. 4.** Frequency-specific associations between verbal working memory and auditory steady state response (ASSR). (A) In schizophrenia spectrum disorder patients, higher 2.5 Hz ASSR was associated with better working memory. (B) In first-degree relatives, 40 Hz ASSR was associated with working memory. (C) The ASSR–working memory relationships (by their correlation coefficients: $y$ axis) were strongly (negatively) associated with stimulus frequencies.

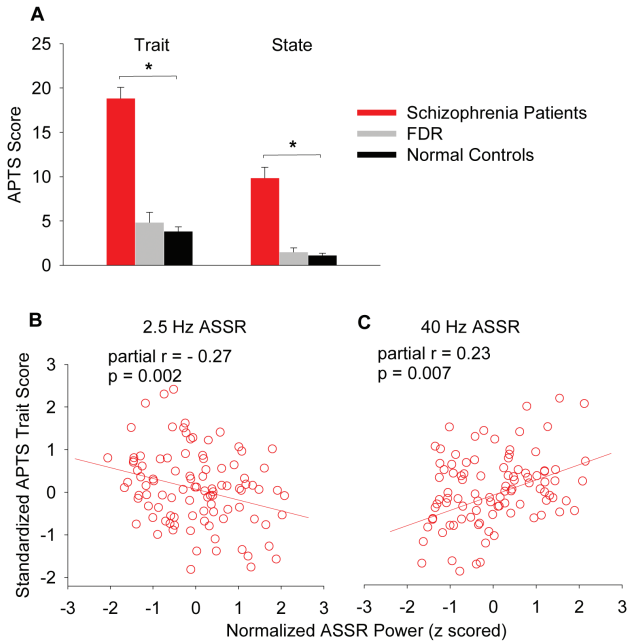


**Fig. 5.** Auditory perception as measured by Auditory Perceptual Trait and State Scale was significantly higher (*) in patients compared with controls as experience in lifetime (trait) or the past 7 days (state), but not in first-degree relatives compared with controls (A) Regression analyses reviewed that 2.5 Hz (B) and 40 Hz (C) auditory steady state response contributed to auditory perceptual trait score in patients but in opposite directions. Partial *r* refers to having partialled out the effects of 2.5 Hz for 40 Hz, or vice versa, in the regression analyses.

### *Medication and Other Clinical Measurements*

Chlorpromazine equivalent (CPZ) of antipsychotic dosages was not correlated with ASSR power at any frequency (all $r < .13$, all $P > .20$). BPRS total or psychosis score was not significantly correlated with ASSR power at any frequency (all $r < .11$, all $P > .30$).

## Discussion

We found that delta and gamma ASSR were both reduced in patients, with delta showing a more pronounced reduction. Critically, reduced delta ASSR was associated both with more severe longitudinally experienced auditory symptom "traits" and also poorer VWM. The observed reduction in gamma ASSR, on the other hand, which was also present in nonpsychotic FDR, was found to be more associated with the risk of SSD than with SSD itself.

The finding of reduced 40 Hz ASSR in SSD replicates other studies[3,23,24,45] while the finding of reduced delta ASSR is new. While delta band power may be significantly increased in SSD in resting EEG,[46] delta band oscillations in SSD are also found to be significantly reduced in stimulus or behavior activated paradigms.[22,47–53] Of particular relevance are findings of reduced delta power and fronto-temporal coherence during talking[51] and auditory target detection[52] in SSD. Unlike a task-related auditory paradigm depending on performance, the delta ASSR is a passive paradigm and its deficit may indicate difficulty in generating normal delta synchronization to auditory stimuli. Reduced ability to generate delta entrainment might serve as a tangible mechanism for the frequently observed auditory–verbal domain issues in SSD, as neural entrainment in the delta and theta band is critical for normal speech perception.[12–14]

Auditory hallucinations are experienced by most patients with SSD in their lifetime.[54,55] We tested the hypothesis that an ASSR delta deficit contributes to their auditory symptoms, as low frequency temporal modulations (<4 Hz) are more critical in speech perception than faster (22–40 Hz) modulations.[12–14] This hypothesis was supported. Patients have impaired ability to generate delta ASSR more so than any other frequency tested, and this deficit is associated with more severe longitudinally experienced auditory anomalies. We did not find this correlation with "state" symptoms in APTS or BPRS, perhaps due to fluctuations in state symptoms or to variability in treatment or treatment response.

ASSR-based delta entrainment was significantly associated with VWM (figure 4A). The linear relationship between stimulus frequency and the ASSR–VWM correlation coefficients ($r = -.95$; figure 4C) further highlights a potentially prominent role of low frequency oscillations in the auditory cognitive system in patients with SSD.

In evaluating the association between ASSR power and VWM, we observed that the most strongly correlated frequency band changed from delta with SSD to gamma with FDR (figure 4A vs figure 4B). In the auditory cortex, the amplitude of neural oscillations are controlled in a nested fashion, where delta (1–4 Hz) phase modulates theta (4–8 Hz) amplitude, and theta phase modulates gamma (30+ Hz) amplitude.[56] This oscillatory hierarchy is thought to control baseline excitability.[56] Under this assumption, we speculate that in individuals without a major deficit in delta generation, as in FDR, gamma band abnormality may yield a more apparent relationship with VWM (figure 4B). However, in individuals with major deficits in delta generation, as in the patients, delta deficits may exert a more fundamental role and thus stronger contribution to VWM (figures 4A and 4C).

Figure 2 illustrates the "preferential" entrainment at 2.5 and 40 Hz using absolute power analysis even at a single electrode. The special 40 Hz entrainment in human brains is well known but the 2.5 Hz case is a new observation. Using normalization and DSS analysis, the reduction of 2.5 Hz ASSR for SSD was significant, but not when using simple spectral power; this may explain the lack of earlier observations. DSS and normalization reduce variability separately in delta ASSR (normalization does not improve gamma ASSR), allowing the delta reduction to even surpass the gamma reduction.

Delta ASSR was not significantly different between FDR and controls, suggesting that this deficit does not

indicate a genetic vulnerability for SSD. The finding of reduced 40 Hz ASSR in FDR replicated our previous finding,[27] now in an independent, much larger cohort. Combined with another independent replication,[29] the data support a 40 Hz ASSR deficit as a genetic biomarker for SSD.

Greater 40 Hz ASSR (within overall reduction) in patients was associated with more auditory symptoms (figure 5C). This matches findings in the visual domain, where higher gamma during gestalt perception was associated with more visual hallucinations.[57] Recent animal and human studies are converging to show that glutamatergic receptor antagonists increase gamma neural oscillations.[58,59] A leading hypothesis in psychosis generation is excitatory glutamatergic receptor hypofunction, based on observations that glutamatergic receptor antagonism by phencyclidine and ketamine mimics aspects of schizophrenia symptomatology.[60,61] Therefore, the link between higher gamma power and more visual and auditory symptoms could be through abnormal glutamatergic mechanisms.

Gamma oscillations are generated by inhibitory GABAergic interneurons regulating excitatory glutamatergic pyramidal neurons.[62,63] Abnormal GABAergic regulation of gamma is thought to underlie working memory deficits in SSD[64–66] and is often hypothesized to be genetic in origin.[67] Therefore, reduced gamma ASSR in FDR, and correlation with working memory in FDR (figure 4B), appear to support the hypothesis that gamma-working memory deficit confers risk for SSD. The neural mechanisms underlying delta oscillations are less well understood. Studies of sleep and waking state delta oscillations[68] suggest that NMDA receptors play a role in maintaining these slow oscillations, and the NMDA receptor antagonist ketamine reduces slow wave 1–5 Hz oscillations.[58] Whether reduced delta ASSR reflects an NMDA hypofunction origin of schizophrenia[69] would require follow-up studies.

Compared to conventional single-channel-based spectral power analysis, this study employed the techniques of DSS, which integrates over channels, and normalization, which takes into account background power; both contribute separately to increase statistical power in the ASSR analysis. Normalization particularly improves ASSR analysis at lower frequencies, due to the 1/f nature (strong rise at low frequencies) of noisy background activity in electrophysiological recordings.[70,71] DSS enhances amplitude contrast, due to its ability to optimally combine responses across electrodes and so extract ASSR responses with higher fidelity. DSS performs only spatial, not spectral filtering, and hence does not introduce artifacts associating with spectral filtering.

An important limitation is that we did not test for the specificity of the findings. We tested auditory working memory, but not deficits in other cognitive domains. This limits interpretation regarding whether the correlations with clinical features were specific to auditory working memory or more general to other cognitive deficits. Reduced delta frequency ASSR in SSD might also arise from antipsychotic medications, though no correlations were found between delta frequency ASSR and current antipsychotic medication dosage. Finally, the failure to synchronize to delta frequency stimulation could also be related to abnormal baseline delta activity, although the DSS procedure was designed to account for this effect.

In summary, the results from this study support that inadequate ability to sustain neural oscillatory responses in the lower frequency range may play a role in the auditory perceptual and cognitive deficit mechanisms in schizophrenia. The findings from this study support the use of delta range ASSR as part of the effort to build translational animal models to study the etiology of SSD.

## Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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