Hierarchical Organization of Gamma and Theta Oscillatory Dynamics in Schizophrenia

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Background: Schizophrenia patients have deficits across a broad range of important cognitive and clinical domains. Synchronization of oscillations in the gamma frequency range (~40 Hz) is associated with many normal cognitive functions and underlies at least some of the deficits observed in schizophrenia patients. Recent studies have demonstrated that gamma oscillations are modulated by the phase of theta waves, and this cross-frequency coupling indicates that a complex and hierarchical organization governs neural oscillatory dynamics. The aims of the present study were to determine if schizophrenia patients have abnormalities in the amplitude, synchrony, and cross-frequency coupling of gamma and theta oscillations in response to gamma-frequency steady-state stimulation and if abnormal neural oscillatory dynamics are associated with cognitive deficits in schizophrenia.

Methods: Schizophrenia patients ($n = 234$) and healthy control subjects ($n = 188$) underwent electroencephalography testing in response to 40-Hz auditory steady-state stimulation. Cognitive functions were assessed with a battery of neuropsychological tests.

Results: Schizophrenia patients had significantly reduced gamma intertrial phase coherence, increased theta amplitude, and intact cross-frequency coupling relative to healthy control subjects. In schizophrenia patients, increased theta amplitude was associated with poor verbal memory performance.

Conclusions: Results suggest that schizophrenia patients have specific alterations in both gamma and theta oscillations, but these deficits occur in the context of an intact hierarchical organization of their cross-frequency modulation in response to 40-Hz steady-state stimulation. Cortical oscillatory dynamics may be useful for understanding the neural mechanisms that underlie the disparate cognitive and functional impairments of schizophrenia.

Key Words: Auditory steady-state response, cross-frequency coupling, gamma oscillations, neural oscillations, schizophrenia, theta oscillations

Schizophrenia patients have deficits in many domains ranging from abnormalities in basic sensory registration to impairments in higher cognitive operations (1) that are associated with poor long-term functional outcome (2,3). Deficits in early sensory processing have also been extensively documented in schizophrenia using a variety of neurophysiological and neuroimaging techniques (4). These deficits serve as endophenotypes in genetic studies (5) and biomarkers in pharmacologic studies (6).

Neural oscillations in gamma band (30–80 Hz) have been proposed to play an important role in information processing (7). Gray and Singer (8) reported that in the cat visual cortex, the firing probability of neurons in response to visual stimuli oscillated in gamma frequency range. The neuronal firing pattern was tightly correlated with oscillatory activity of local field potential (LFP). Tallon-Baudry *et al.* (9) reported that gamma oscillations in human scalp electroencephalography (EEG) reflected visual perception. These findings led to the suggestion that the oscillatory pattern of neuronal firing represents information processing associated with not only visual perception but also other cognitive domains and reflected in EEG. Recent studies have shown that gamma oscillations in neuronal firing, LFP, intracranial EEG, and scalp EEG are associated with a variety of sensory and cognitive processes, including perception (9,10), attention (11,12), memory (13,14), and working memory (15)—all domains in which schizophrenia patients exhibit deficits (1,16,17). In addition, schizophrenia patients show abnormal gamma oscillations in perception (18,19), sensory gating (20), backward masking (21), selective attention (22), working memory (23), and cognitive control (24). While some studies have found reduced power and phase synchronization of gamma oscillations in schizophrenia, others reported increased power of gamma oscillations in schizophrenia (25,26). These discrepancies suggest that the type of abnormal gamma oscillations depends on the cognitive tasks and oscillatory parameters under investigation.

Since gamma oscillations are associated with important cognitive operations and are generated by interneurons and pyramidal cells in cortical networks (27–29), it is possible that abnormalities in the ability of neural circuits to support this critical frequency range might represent a fundamental deficit of schizophrenia (30,31). It is important to note, however, that gamma oscillations interact with neural oscillations in other frequency bands (32). For example, emerging evidence has shown that gamma oscillations are modulated by neural oscillations in lower (e.g., theta) frequency bands (33,34). This is termed cross-frequency coupling. While there are several types of cross-frequency coupling, phase-amplitude cross-frequency coupling has been proposed to play an important role in information processing (35). Phase-amplitude cross-frequency coupling indicates that the phase of lower-frequency oscillations modulates the amplitude of higher frequency oscillations (Figure 1). In particular, phase-amplitude cross-frequency coupling between theta and gamma oscillations has been observed in LFP (34), intracranial EEG (33), and scalp EEG (36). Since theta oscillations have large temporal and spatial scales and gamma oscillations have small temporal and spatial scales (37), cross-frequency coupling may represent the integration of information processed across different temporal and spatial scales and has been observed during visual perception (36) and working memory (38) in nonpsychiatric subjects.

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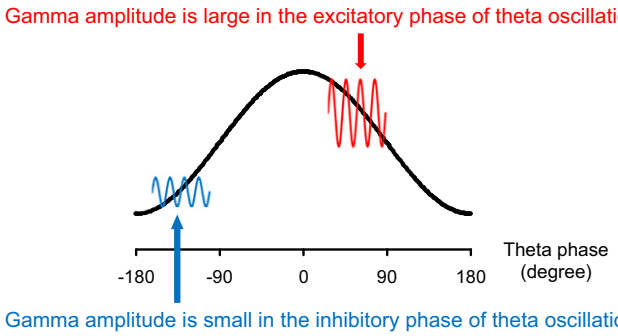

Figure 1. Heuristic model of phase-amplitude cross-frequency coupling. Gamma oscillations (red and blue lines) are largest in the excitatory versus inhibitory phase of ongoing theta oscillations (black line). Note that excitatory and inhibitory phase may vary according to tasks and neural sources.

Several models of cross-frequency coupling have been proposed, although the underlying neural mechanisms remain to be elucidated. Because the phase of neural oscillations in LFP modulates the probability of neuronal firings (34), cross-frequency coupling indicates that the phase of low-frequency oscillations modulates the excitability of high-frequency oscillations. In this context, low-frequency oscillations are entrained by rhythmic external stimuli and align the excitatory phase with attended stimuli (39). This "oscillatory selection" (40) model might explain the association between cross-frequency coupling and sensory processing. In contrast, the "phase coding" (41) model suggests that each memory is represented by a gamma cycle, whereas a sequence of memories is represented by several gamma cycles nested within one theta cycle (42). This phase coding model might explain the association between cross-frequency coupling and working memory.

Cross-frequency coupling indicates that neural oscillations have a complex and hierarchical organization. Accordingly, abnormal gamma oscillations in schizophrenia patients may represent only a part of the complex constellation of deficits in neural oscillatory dynamics that give rise to deficits in cognitive functions. Spencer *et al.* (43) reported abnormal cross-frequency interactions between delta phase and gamma phase locking factor but did not investigate phase-amplitude cross-frequency coupling. Conversely, Allen *et al.* (44) reported abnormal phase-amplitude cross-frequency coupling between different frequency bands but did not investigate other aspects of neural oscillations such as power and intertrial phase coherence (ITC) that are impaired in schizophrenia (45,46).

In this study, we investigated gamma and theta oscillations, as well as theta-gamma phase-amplitude cross-frequency coupling, in schizophrenia in response to 40-Hz (i.e., gamma frequency) auditory steady-state stimuli. This paradigm assesses the capacity to support stimulus-driven, gamma oscillations. Auditory steady-state responses (ASSRs) are largest in response to 40-Hz stimulation (47) and are suitable for cross-species translational studies since rodents demonstrate homologous responses (48). Many studies have demonstrated that schizophrenia patients have robust deficits of gamma oscillations in this paradigm (43,46,49,50), although theta oscillations and cross-frequency coupling have not been previously examined in this context. We therefore hypothesized that schizophrenia patients would exhibit separate abnormalities in both gamma and theta oscillations, as well as decreased theta-gamma cross-frequency coupling. In the present study, amplitude and ITC were selected as the primary measures of neural oscillations. Amplitude and ITC reflect complementary aspects of neural oscillatory dynamics and represent distinct alterations in schizophrenia (51). We also hypothesized that abnormalities in these oscillations would be associated with cognitive deficits in schizophrenia patients.

Methods and Materials

Subjects

Subjects included 234 schizophrenia patients and 188 healthy control subjects (Table 1). Evoked gamma power and ITC from a subset of these participants were previously published (46). All participants were assessed on their capacity to provide informed consent, and after detailed description of study procedures were provided, written consent was obtained per University of California, San Diego Institutional Review Board approved forms (IRB# 030510). All subjects received a urine toxicology screen to rule out

Table 1. Demographic, Clinical, and Cognitive Characteristics of the Subjects

Characteristic	HC (n = 188)	SZ (n = 234)	Statistic	p
Sex (Male/Female)	94/94	182/52	$\chi^2 = 35.55$	<.001
Age (Years)	43.9 (11.1)	44.5 (8.8)	$F(1,418) = 1.13$	.29
Duration of Illness (Years)		22.7 (9.9)		
SAPS Score		8.7 (4.1)		
SANS Score		13.7 (4.5)		
GAF Scale Score		41.2 (7.1)		
WRAT-3				
Reading total score	51.0 (4.8)	44.2 (7.1)	$F(1,418) = 105.61$	<.001
CVLT-2				
List A trial 1–5	51.7 (10.9)	35.3 (10.8)	$F(1,418) = 188.09$	<.001
Long-delay free recall	11.6 (3.2)	7.2 (3.4)	$F(1,418) = 150.52$	<.001
WCST-64				
Perseverative responses	11.0 (7.8)	21.6 (17.6)	$F(1,418) = 46.69$	<.001
Categories completed	3.2 (1.5)	2.0 (1.5)	$F(1,418) = 52.48$	<.001
LNS				
Forward	14.0 (2.9)	11.7 (3.1)	$F(1,418) = 56.97$	<.001
Reorder	10.8 (2.4)	8.0 (2.5)	$F(1,418) = 127.41$	<.001

CVLT-2, California Verbal Learning Test, 2nd Edition; GAF, Global Assessment of Functioning; HC, healthy control subjects; LNS, Letter-Number Sequencing; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SZ, schizophrenia patients; WCST-64, Wisconsin Card Sorting Test-64 Card Version; WRAT-3, Wide Range Achievement Test, 3rd Edition.

recent drug use. In addition, all subjects were carefully screened with the use of the Structured Clinical Interview for DSM-IV to ensure that they did not have an Axis I diagnosis other than schizophrenia (52) and had not experienced a neurologic insult, such as significant head trauma and/or loss of consciousness. Audiometric testing was used to ensure that all participants could detect 1000-Hz tones at 40 dB.

Healthy control subjects were recruited through newspaper and internet advertisements. Schizophrenia patients were recruited from community residential facilities and via physician referral. Antipsychotic medications were prescribed for 218 schizophrenia patients. In schizophrenia patients, clinical symptoms were assessed with the Scale for the Assessment of Negative Symptoms (53) and the Scale for the Assessment of Positive Symptoms (54). The current level of functioning was assessed with the modified Global Assessment of Functioning (55).

Cognitive Tasks

The Wide Range Achievement Test 3 reading subtest was used to estimate premorbid verbal abilities (56). Verbal memory was assessed via the California Verbal Learning Test-2 (CVLT-2) List A 1 to 5 total score and delayed free recall indices (57). Perseverative responses and number of categories completed on the Wisconsin Card Sorting Test were used to assess concept formation and conceptual flexibility (58). Performance on the Letter-Number Sequencing test was used to assess the immediate online storage and repetition of auditory information (forward condition), as well as working memory via manipulation and retrieval of stored information (reordering condition) (59,60).

Stimuli

Auditory steady-state stimuli were presented to subjects by means of foam insert earphones (Model 3A; Aearo Company Auditory Systems, Indianapolis, Indiana). The stimuli were 1-millisecond, 93-dB clicks presented in 500-millisecond trains varying in rate of presentation (20, 30, and 40 Hz) in each of three blocks (order fixed). Blocks contained 200 trains of clicks with 500-millisecond intervals.

EEG Recording

Electroencephalography recordings were acquired with a Neuroscan Nuamp system (Neuroscan Laboratories, El Paso, Texas). The EEG was recorded from the scalp through 34 sintered silver/silver chloride electrodes with the use of an electrode cap (EasyCap; Falk Minow Services, Herrshing-Breitbrunn, Germany). Electrodes placed at the tip of the nose and at Fpz served as the reference and ground, respectively. Four additional electrodes placed above and below the left eye and at the outer canthi of both eyes were used for monitoring blinks and eye movements. All impedances were below 4 kΩ. Signals were digitized at a rate of 1000 Hz with system acquisition filter settings at .5 Hz to 100 Hz. Electroencephalography and stimulus markers were recorded continuously. Subjects did not smoke for at least 60 minutes before EEG testing and were instructed to minimize eye movements and muscle artifact during the recording. During testing, subjects were observed through a one-way mirror. In addition, signal quality and the number of sweeps free of gross artifacts (defined as ± 100 μV across the 0–512 milliseconds after stimuli) were closely monitored.

EEG Analyses

Electroencephalography preprocessing was performed offline with BrainVision Analyzer (Brain Products GmbH, Gilching, Germany). Continuous data in response to 40-Hz stimulation were segmented relative to the onset of stimuli (−1.5 to 1.5 seconds). Segmented data were mathematically corrected for eye movement artifact with an established method (61). After blink correction, epochs containing $> \pm 100$ μV were automatically rejected. Epochs were also manually reviewed to reject EEG epochs with other artifacts (e.g., muscle activity).

Time-frequency analyses were performed with EEGLAB (62) and MATLAB (Mathworks, Natick, Massachusetts). Data at Fz were used for further analyses because this is the electrode with maximal responses (46,49). We selected 100 artifact-free epochs randomly from each subject and used them for further analyses, since the number of epochs can impact signal-to-noise ratios and ITC measures. First, the raw signals were filtered with central frequencies from 6 Hz to 50 Hz, in 2-Hz steps with 4-Hz bandwidth. A two-way least squares finite impulse response filter (eegfilt.m in EEGLAB) was used because this filtering method does not distort phase (63). Second, a Hilbert transform was applied to the filtered signals. Third, amplitude, phase, and ITC were calculated from Hilbert transformed signals. Amplitude indicates the total amplitude including prestimulus baseline activity and event-related spectral perturbations. Intertrial phase coherence indicates phase consistency across trials and ranges from 0 (random phase across trials) to 1 (identical phase across trials). Amplitude and ITC during stimulation were averaged and used for statistical analyses (Figure S1 in Supplement 1).

For analysis of cross-frequency coupling, we focused on theta (4–8 Hz) and gamma oscillations (38–42 Hz), since previous studies (33,34,36,38) showed that phase of theta oscillations modulated amplitude of gamma oscillations. Theta phase and gamma amplitude during stimulation from all epochs were concatenated in each subject. Gamma amplitude was sorted according to theta phase. Theta phase was divided into six bins of 60° (−180 to −120, −120 to −60, −60 to 0, 0 to 60, 60 to 120, and 120 to 180). Mean gamma amplitude was calculated in each bin. We compared gamma amplitude in each bin of theta phase using analysis of variance (ANOVA). A modulation index (33) was computed to quantitatively assess the strength of cross-frequency coupling. Gamma amplitude was divided by the mean gamma amplitude to obtain an index of relative gamma amplitude in each subject, since large gamma amplitude produces large modulation indices regardless of cross-frequency coupling strength (64). We composed a complex-valued signal z by combining relative gamma amplitude A_{GA} with theta phase Θ_{TH}: $z = A_{GA}\, e^{i\Theta_{TH}}$. A complex value of z at each time point was plotted in the complex plane (Figure S2 in Supplement 1). The average of z at all time points was calculated and shown as a mean vector. The modulation index is the length of the mean vector. Identical procedures were used for surrogate data that was created by pairing theta phase with gamma amplitude from randomly shuffled trials. We used the modulation index from surrogate data to differentiate true cross-frequency coupling with spurious cross-frequency coupling. Log transformation of the modulation index was used for statistical analysis as reported by Penny *et al.* (65).

Statistical Analyses

Statistical analyses were performed with PASW Statistic (IBM Corporation, Somers, New York). Chi-square tests were used to assess differences in sex distribution. Age effects were assessed using two-way (group-by-sex) ANOVA. Differences in clinical symptoms between sexes in schizophrenia patients were assessed with *t* tests. Differences in neuropsychological performances and amplitude and ITC of neural oscillations were assessed with two-way (group-by-sex) ANOVA. Cross-frequency coupling was analyzed in a repeated-measures ANOVA with group and sex as between-subjects factors and theta phase as a within-subjects factor with Greenhouse-Geisser epsilon adjustment. The modulation index was ana-

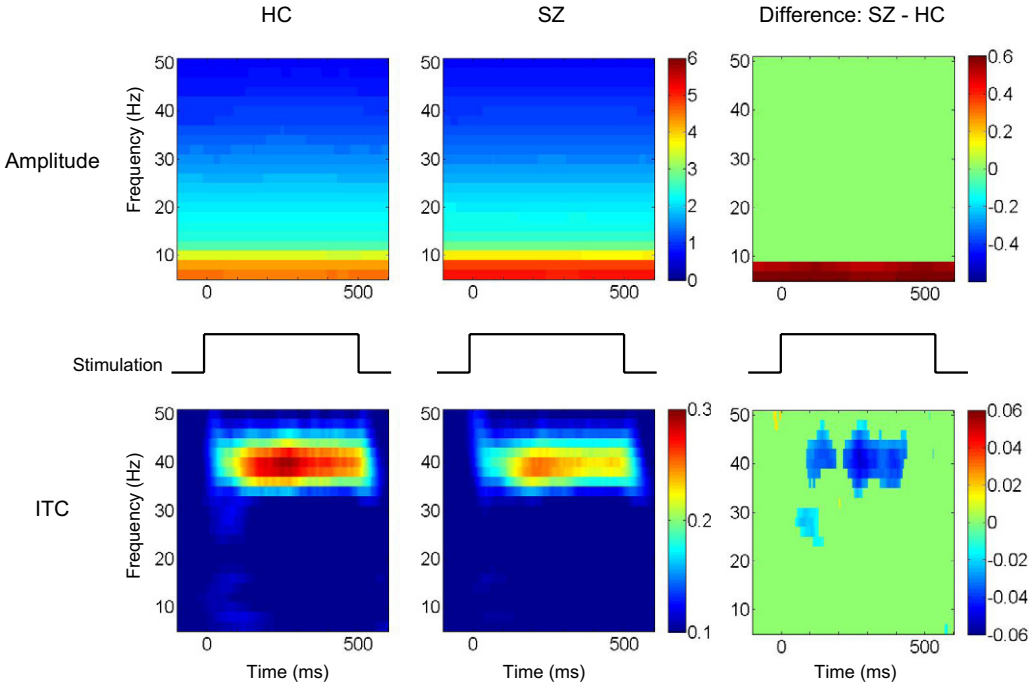

Figure 2. Schizophrenia patients (SZ) have increased theta amplitude and decreased gamma synchrony. The left column shows time-frequency maps from healthy control subjects (HC) and the middle column shows time-frequency maps from schizophrenia patients. The x axis indicates time in milliseconds and the y axis indicates frequency. Color indicates amplitude in the top row and intertrial phase coherence (ITC) in the bottom row. The right column shows difference between schizophrenia patients and healthy control subjects. Difference maps show only time-frequency points at $p < .01$.

lyzed in a repeated-measures ANOVA with group and sex as between-subjects factors and data (observed data and surrogate data) as a within-subjects factor. Spearman correlations were performed to assess the relationships of EEG measures to cognitive measures. Differences in correlation coefficients between groups were assessed with Fisher's *Z* transformation. All statistical comparisons were two-tailed with α-level = .05. We used Bonferroni correction to correct for the effect of multiple comparisons in neural oscillations (six ANOVAs [theta amplitude, theta ITC, gamma amplitude, gamma ITC, cross-frequency coupling, modulation index]: $p = .05/6 = .008$), neuropsychological performances (seven ANOVAs: $p = .05/7 = .007$), and their correlations (7 cognitive measures $\times$ 5 EEG measures [theta amplitude, theta ITC, gamma amplitude, gamma ITC, modulation index] = .05/35 = .001).

Results

Sample Characteristics

Table 1 shows demographic, clinical, and cognitive characteristics of the subjects. There was a greater proportion of male subjects among schizophrenia patients than among healthy control subjects. Analyses of age revealed no significant effects of group or sex or no significant group-by-sex interaction [$F(1,418) < 1.71, p > .19$]. There were no significant differences in age, duration of illness, Scale for the Assessment of Positive Symptoms, Scale for the Assessment of Negative Symptoms, and Global Assessment of Functioning [$-1.20 < t(232) < .82, p > .23$] between male and female schizophrenia patients.

Compared with healthy control subjects, schizophrenia patients had significantly worse performance in all of the neuropsychological tests. Analyses of performance in neuropsychological tests revealed significant effects of sex in CVLT-2 List A trial 1 to 5 total score (female > male) [$F(1,418) = 8.93, p = .003$]. There were no other significant effects of sex or no significant group-by-sex interactions in neuropsychological tests [$F(1,418) < 3.82, p > .05$].

Theta and Gamma Oscillations

Figure 2 shows time-frequency maps. In the exploratory analysis, *t* tests revealed differences ($p < .01$) between groups in both theta and gamma frequency responses. Thus, theta oscillations (4–8 Hz) and gamma oscillations (38–42 Hz) served as the focus of further analyses.

Schizophrenia patients had significantly larger theta amplitude and smaller gamma ITC compared with healthy control subjects (Table 2). There were no significant group differences in either theta ITC or gamma amplitude. Analysis of theta and gamma oscillations revealed significant effects of sex in theta amplitude (female > male) [$F(1,418) = 19.48, p < .001$] and in gamma amplitude (female > male) [$F(1,418) = 17.45, p < .001$]. There were no significant sex differences or no significant group-by-sex interactions in theta ITC and gamma ITC [$F(1,418) < 3.67, p > .06$].

Analysis of cross-frequency coupling (Figure 3) revealed a significant main effect of theta phase on gamma amplitude [$F(5,2090) = 39.66, p < .001$]. Theta phase showed no significant interactions with group, sex, or group-by-sex [$F(5,2090) < 1.31, p > .27$]. These results indicate that theta phase modulates gamma amplitude in both healthy control subjects and schizophrenia patients. Because we found significant cross-frequency coupling, we used a modulation index to analyze the strength of cross-frequency coupling. The modulation index from the observed data was significantly larger than the modulation index from surrogate data [$F(1,418) = 7.04, p = .008$], indicating significant cross-frequency coupling (Figure 4).

Table 2. Amplitude and Intertrial Phase Coherence of Theta and Gamma Oscillations

EEG Variables	HC (n = 188)	SZ (n = 234)	F(1,418)	p
Theta Amplitude (μV)	4.493 (1.483)	5.091 (2.240)	22.09	<.001
Theta ITC	.100 (.032)	.095 (.031)	1.58	.21
Gamma Amplitude (μV)	1.050 (.260)	1.054 (.321)	1.34	.25
Gamma ITC	.251 (.101)	.220 (.093)	10.00	.002

Data are given as mean (SD).

EEG, electroencephalography; HC, healthy control subjects; ITC, intertrial phase coherence; SZ, schizophrenia patients.

Analysis of the modulation index revealed no significant effects of group or sex or no significant interactions [$F(1,418) < 2.23, p > .14$]. These results indicate that there is significant cross-frequency coupling in both healthy control subjects and schizophrenia patients and that there is no group difference in strength of cross-frequency coupling.

Neural Oscillations and Cognitive Measures

Theta amplitude was significantly correlated with CVLT-2 List A trial 1 to 5 total score in schizophrenia patients ($r_s = -.36, p < .001$) but not in the healthy control subjects ($r_s = -.10, p = .19$). The difference in this correlation coefficient between groups was significant ($Z = -4.79, p < .001$). Because there were sex differences in theta amplitude and CVLT-2 List A trial 1 to 5 total score, correlations were separately analyzed for each sex. Theta amplitude was significantly correlated with CVLT-2 List A trial 1 to 5 total score in both male ($r_s = -.38, p < .001$) and female ($r_s = -.46, p < .001$) schizophrenia patients but in neither male ($r_s = .05, p = .64$) nor female ($r_s = .06, p = .58$) healthy control subjects (Figure S3 in Supplement 1). The differences in these correlation coefficients between groups were significant in both male ($Z = -3.45, p < .001$) and female subjects ($Z = -3.09, p = .002$). There were no other significant correlations between EEG measures and cognitive measures.

Discussion

The results of the present study demonstrate that schizophrenia patients exhibit increased theta amplitude and reduced gamma intertrial phase coherence during auditory steady-state stimulation. In addition, theta phase modulates gamma amplitude, and theta amplitude correlates with verbal memory performance. The finding of normal theta-gamma cross-frequency coupling indicates that schizophrenia patients have an intact hierarchical organization of neural oscillatory dynamics that is similar to healthy control subjects, but schizophrenia patients have alterations in several components of this organization, augmenting previous findings that schizophrenia patients have alterations in gamma oscillations (43,46,49,50). To our knowledge, this is the first report of cross-frequency coupling between theta phase and gamma amplitude during auditory steady-state stimulation in schizophrenia patients.

The finding that theta phase modulates gamma amplitude is consistent with previous studies of LFP (34), intracranial EEG (33,38), and scalp EEG (36). Cross-frequency coupling between theta phase and gamma amplitude has been observed in hippocampus (38) and cerebral cortex (33), including auditory cortex (34) where ASSRs are generated (43,66). Gamma amplitude was largest at approximately 60° of theta phase, consistent with some studies (34,36), but not all studies that also reported that gamma amplitude was largest in 0° (38) or 180° (33) of the theta phase. Such discrepancies suggest that the excitatory phase for surface-recorded gamma oscillations may vary according to the task demands and neural generators of these waveforms.

In contrast to our expectations, schizophrenia patients had no alterations in cross-frequency coupling. This result is unexpected because theta-gamma phase-amplitude cross-frequency coupling is thought to play a critical role in sensory and cognitive operations. Nonetheless, schizophrenia patients did exhibit abnormalities in both theta and gamma components in the context of an apparently intact hierarchical organization of neural oscillations. Because several factors such as signal-to-noise ratio can influence the measurement of cross-frequency coupling (64,65), it is possible that abnor-

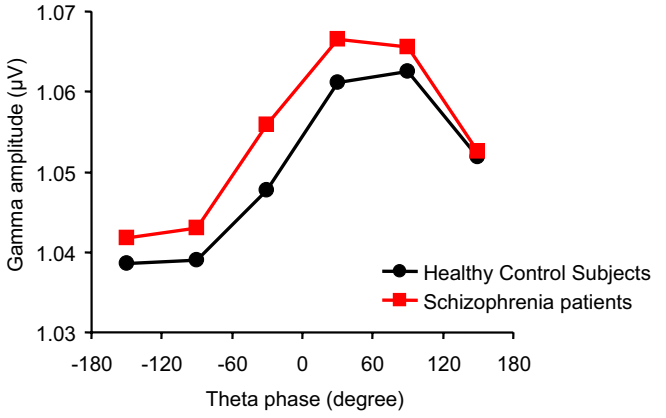

Figure 3. The amplitude of stimulus-driven gamma oscillations is modulated by the phase of ongoing theta oscillations. This cross-frequency coupling indicates a hierarchical organization of cortical oscillatory dynamics in both healthy control subjects (black line) and schizophrenia patients (red line). The x axis indicates theta phase. The y axis indicates gamma amplitude.

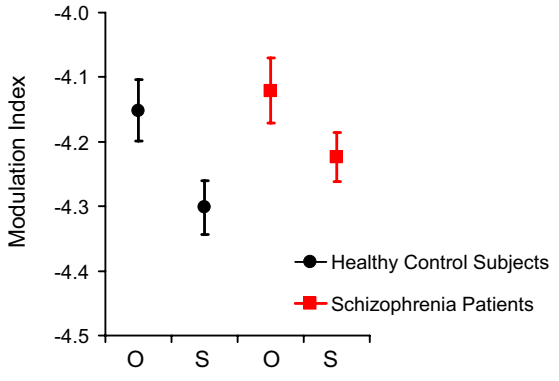

Figure 4. Schizophrenia patients have normal theta-phase/gamma-amplitude cross-frequency coupling. The modulation index demonstrates the relative strength of cross-frequency coupling via comparison of observed (O) versus resampled or surrogate (S) electroencephalography data in healthy control subjects (black circle) and schizophrenia patients (red squares). The y axis indicates log transform of modulation index.

malities in theta and/or gamma oscillations may affect the finding of normal cross-frequency coupling in schizophrenia. The inability to detect significant deficits in cross-frequency coupling, however, does not appear to be due to methodological limitations, since two different methods revealed a similar pattern of results—normal cross-frequency coupling in schizophrenia patients. In contrast, the failure to detect abnormalities in cross-frequency coupling may be due to the simple and passively elicited ASSR task used in this study, which does not require the substantial engagement of neural circuits associated with higher order and integrative cognitive mechanisms. Thus, this paradigm may not be optimal for revealing cross-frequency coupling deficits, since the present study of 422 individuals was adequately powered to detect even small effect-size differences. Since cross-frequency coupling may be task-dependent, the present results do not preclude the possibility that schizophrenia patients may have cross-frequency coupling abnormalities in tasks that depend upon more distributed neural systems.

The finding of increased theta amplitude in schizophrenia patients is consistent with previous studies that showed augmented resting state theta power in schizophrenia (45). In the present study, increased theta amplitude was associated with worse verbal memory performance in schizophrenia patients. Increased theta amplitude in schizophrenia patients is present in the temporal lobe (67), including the auditory cortex (68,69), where schizophrenia patients show decreased gray matter volume (70). Therefore, abnormal theta amplitude may reflect pathological processes that are associated with verbal memory deficits in schizophrenia.

Important sex differences were also revealed in the present study. Female subjects showed increased theta amplitude relative to male subjects in both schizophrenia patients and healthy control subjects. Female subjects also showed better verbal memory performance relative to male subjects in both schizophrenia patients and healthy control subjects. The sex difference in theta amplitude, however, does not account for the observed sex differences in verbal memory performance, since theta amplitude was not associated with verbal memory performance in healthy control subjects and increased theta amplitude was associated with worse verbal memory performance in schizophrenia patients. Additional studies of potential sex difference in neural activity associated with theta oscillations are necessary to fully explain the present pattern of results.

The finding of reduced gamma ITC in schizophrenia patients is consistent with previous studies (43,46,50). Reduced gamma ITC indicates that gamma phase at a given latency is inconsistent across trials. Imprecise gamma phase synchronization in schizophrenia may affect various sensory and cognitive processes since gamma phase modulates firing rates of neurons (71) and neuronal interactions (72). In contrast to our expectations and previous results (46), no significant correlations were observed between reduced gamma ITC and cognitive functions in this study. As noted above, this may be due to the task used in this study. Gamma ITC during auditory steady-state stimulation may not fully engage neural networks associated with higher cognitive functions because the auditory steady-state task is a passive task and ASSRs are predominantly generated in the auditory cortex (43,66). Gamma amplitude did not differ between groups but showed a difference between sexes with female subjects producing larger gamma amplitude compared with male subjects, consistent with a previous study (73).

There are several limitations in this study. First, medications were not experimentally controlled in the current study. Schizophrenia patients were treated with a variety of antipsychotic and other psychiatric medications that may affect neural oscillations (74). Prospective studies are needed to clarify potential medication effects on neural oscillations and to further validate the use of oscillatory measures as biomarkers of drug response. Second, it is possible that small eye movements during testing (i.e., microsaccades) may have influenced the results of this study. Saccades can generate spurious gamma band activity in scalp EEG (75). Microsaccade artifact, however, results in broadband and transient increases in power, whereas auditory steady-state stimulation occurs in response to a narrow band of stimulation and results in continuous increases in power and ITC. Nevertheless, gamma amplitude and cross-frequency coupling may be affected by saccades. To account for this possibility, we performed the same analyses on the horizontal electrooculogram—no significant main effects or interactions in gamma amplitude or cross-frequency coupling (all $F < 2.02$, all $p > .13$) were present, highly reducing the likelihood of prominent saccade-induced artifact contamination oscillatory dynamics. Third, delta oscillations were not analyzed in this study, since we could not apply the methods used in this study to delta oscillations, given the long epochs (i.e., >9 seconds) of artifact-free EEG segments required to measure delta activity with confidence in the current recordings. Delta phase may also be coupled with gamma amplitude since delta oscillations are entrained by rhythmic external stimuli and align the excitatory phase with attended stimuli (39). Thus, future studies are needed to assess delta-gamma cross-frequency coupling in schizophrenia.

In conclusion, schizophrenia patients had intact cross-frequency coupling, increased theta amplitude, and reduced gamma intertrial phase coherence. These findings suggest that schizophrenia patients have alterations in gamma and theta oscillations. Despite the deficits in gamma and theta oscillations, a hierarchical organization of neural oscillations is relatively preserved in schizophrenia patients in response to gamma frequency stimulation. Neural oscillations in different frequency bands are associated with distinct aspects of cognitive information processing. The interactions among different frequency bands appear to serve integrative cognitive functions. Future studies are needed to disentangle potential frequency-specific neural oscillatory alternations in schizophrenia under a variety of cognitive challenges and across the course of schizophrenia.

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