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Reduced Natural Oscillatory Frequency of Frontal Thalamocortical Circuits in Schizophrenia

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Context: Converging evidence from electrophysiological studies suggests that in individuals with schizophrenia, electroencephalographic frontal fast oscillations are reduced. It is still unclear whether this reduction reflects an intrinsic deficit of underlying cortical/thalamocortical circuits and whether this deficit is specific for frontal regions. Recent electrophysiological studies in healthy individuals have established that, when perturbed, different brain regions oscillate at a specific, intrinsically generated dominant frequency, the natural frequency.

Objective: To assess the natural frequency of the posterior parietal, motor, premotor, and prefrontal cortices in patients with schizophrenia and healthy control subjects.

Design: High-density electroencephalographic recordings during transcranial magnetic stimulation of 4 cortical areas were performed. Several transcranial magnetic stimulation–evoked electroencephalographic oscillation parameters, including synchronization, amplitude, and natural frequency, were compared across the schizophrenia and healthy control groups.

Setting: Wisconsin Psychiatric Institute and Clinic, University of Wisconsin–Madison.

Participants: Twenty patients with schizophrenia and 20 age-matched healthy control subjects.

Main Outcome Measures: High-density electroencephalographic measurements of transcranial magnetic stimulation–evoked activity in 4 cortical areas, scores on the Positive and Negative Syndrome Scale, and performance scores (reaction time, accuracy) on 2 computerized tasks (word memory [Penn Word Recognition Test] and facial memory [Penn Facial Memory Test]).

Results: Patients with schizophrenia showed a slowing in the natural frequency of the frontal/prefrontal regions compared with healthy control subjects (from an average of a 2-Hz decrease for the motor area to an almost 10-Hz decrease for the prefrontal cortex). The prefrontal natural frequency of individuals with schizophrenia was slower than in any healthy comparison subject and correlated with both positive Positive and Negative Syndrome Scale scores and reaction time on the Penn Word Recognition Test.

Conclusions: These findings suggest that patients with schizophrenia have an intrinsic slowing in the natural frequency of frontal cortical/thalamocortical circuits, that this slowing is not present in parietal areas, and that the prefrontal natural frequency can predict some of the symptoms as well as the cognitive dysfunctions of schizophrenia.

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A DEFECT IN BETA/GAMMA-range frontal electroencephalographic (EEG) oscillations was recently reported by several electrophysiological studies in schizophrenia.[1] In a study comparing neural activity immediately preceding self-generated speech and listening, patients with schizophrenia failed to show an increase in frontal beta-band synchronization (intertrial coherence [ITC]) in the prespeech vs listening condition, and this synchronization deficit was inversely related to hallucination severity.[2] Using a cognitive control task, a study showed that enhanced frontal gamma-band oscillations corresponded to better performance in healthy control subjects, while patients with schizophrenia had reduced frontal gamma activity.[3] Another study using a similar task found that medication-naive and medicated patients with schizophrenia had lower frontal gamma power compared with healthy control subjects and that this reduction predicted worse performance.[4] A study investigating face processing reported reduced frontal gamma-band activity and synchrony in patients with schizophrenia, which was inversely related to their symptoms.[5] Deficits in EEG frontal fast activity and synchronization were also established by using driving auditory stimuli,[6]

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an auditory reaction task,[7] and oddball paradigms in both patients with schizophrenia[8,9] and unaffected identical twins[10] compared with healthy control subjects. Furthermore, by combining transcranial magnetic stimulation (TMS) with high-density (HD) EEG, we recently found that patients with schizophrenia had decreased gamma-band frontal amplitude and synchronization after TMS of the premotor cortex.[11]

An important issue is whether these beta/gamma oscillation deficits are due to an intrinsic defect of the oscillatory properties of cortical/thalamocortical circuits in schizophrenia. Furthermore, if there is such an intrinsic defect, is it specific for frontal circuits or does it extend outside the frontal lobe? Transcranial magnetic stimulation with HD-EEG can be used to probe the functioning of cortical/thalamocortical circuits, and it was recently used to characterize the intrinsic oscillatory frequency, or natural frequency, of such circuits in humans.[12] In a TMS/HD-EEG study in healthy individuals, different brain regions showed a specific natural frequency: α-range oscillations in the occipital cortex, low beta oscillations in the parietal cortex, and high beta/gamma oscillations in the frontal cortex. The study also showed that each brain region maintained its own natural frequency even when activated indirectly after TMS of another cortical area, indicating that the observed oscillations reflected intrinsic, local mechanisms. These findings suggest that the natural frequency is a measure of the intrinsic properties and connections of local cortical/thalamocortical circuits (without necessarily being able to disentangle corticocortical and thalamocortical mechanisms). Importantly, the natural frequency can be assessed without requiring any cognitive engagement and can be measured directly even in frontal brain areas in humans. This is particularly relevant in patients with schizophrenia, in whom the interpretation of reduced fast frontal oscillations is complicated by the presence of cognitive confounds (ie, level of attention, motivation) or by not having direct access to frontal areas.

Herein, we performed TMS/HD-EEG recordings in the posterior parietal, motor, premotor, and prefrontal areas in patients with schizophrenia and healthy control subjects. We hypothesized that frontal areas, but not the parietal cortex, would show an intrinsic defect of their cortical/thalamocortical circuits as reflected by a slowing of their natural frequency. We also expected that the natural frequency slowing would be most prominent in the prefrontal cortex. Finally, we investigated whether prefrontal natural frequency values would correlate with the Positive and Negative Syndrome Scale (PANSS) scores and with accuracy and reaction time in a word memory task and a face memory task in patients with schizophrenia.

METHODS

PARTICIPANTS

Twenty patients with schizophrenia and 20 age-matched healthy control subjects were recruited (**Table 1**). Each participant gave written informed consent, and the study was approved by the University of Wisconsin–Madison Human Subjects Institutional Review Board. A psychiatrist (M.J.P.) interviewed all participants and administered the Structured Clinical Interview for *DSM-IV-TR*[13] to confirm or exclude psychiatric diagnoses. Individuals with schizophrenia were diagnosed as having a paranoid (n=13), undifferentiated (n=3), residual (n=2), or disorganized (n=2) subtype according to *DSM-IV-TR* criteria. Eighteen of the 20 patients were receiving second-generation antipsychotics, while 2 were receiving first-generation antipsychotics. All were outpatients, with a mean (SD) duration of illness of 13 (5) years.

Table 1. Description of Participants

Clinical Variable	Healthy Control Subjects (n=20)	Patients With Schizophrenia (n=20)	*P* Value
Age, mean (SD), y	31.7 (7.8)	32.8 (6.2)	.60
Male/female, No.	16/4	13/7	.31
Positive and Negative Syndrome Scale score, mean (SD)			
Positive		18.0 (6.3)	
Negative		21.5 (5.8)	
General		38.7 (10.8)	

TMS CORTICAL TARGETS

The superior parietal, precentral, superior frontal, and middle frontal gyri, corresponding to the posterior parietal, motor, premotor, and prefrontal areas, were anatomically identified on T1-weighted individual magnetic resonance imaging (MRI), acquired using a 3-T scanner (GE Healthcare) (Talairach coordinates are reported in **Table 2**). These areas were targeted using a Navigated Brain Stimulation system (Nexstim). The Navigated Brain Stimulation system displayed the position of the TMS coil relative to each participant's brain. It also calculated the distance between the scalp underlying the TMS coil and the cortical surface; this scalp to cortex distance was used to estimate the TMS-evoked electric field, expressed in volts per meter, on the cortical areas. In both healthy subjects and patients with schizophrenia, each cortical area was stimulated at 120 V/m, an intensity effective in eliciting EEG oscillations as shown in previous TMS/HD-EEG work.[11,12] This intensity corresponded to 110% to 115% of the resting motor threshold. The resting motor threshold was identified in the right first dorsal interosseus as the TMS intensity required to elicit an electromyographic response of at least 50 μV in 5 of 10 consecutive trials.

HD-EEG RECORDINGS DURING TMS

The TMS-evoked EEG responses were recorded using a TMS-compatible 60-channel amplifier (Nexstim).[14] The EEG signals were referenced to a forehead electrode, high-pass filtered (0.1 Hz), and sampled at 1450 Hz. Two additional sensors were applied to record the electro-oculogram. Because the click associated with the TMS discharge can evoke auditory potentials, a sound masking the TMS click was generated and played via earphones throughout the TMS/HD-EEG sessions (for more details, see the articles by Ferrarelli et al[11] and Massimini et al[15]).

EXPERIMENTAL PROCEDURE

Each participant sat on a reclining chair fitted with a headrest to ensure a stable, comfortable head position throughout the experiment. After preparation for EEG recordings and calibration of the Navigated Brain Stimulation system, TMS sessions were performed. Each session consisted of 200 to 250 TMS

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Table 2. Overall Activity, Duration and Synchronization, and Frequency of Transcranial Magnetic Stimulation–Evoked Electroencephalographic Oscillations in Patients With Schizophrenia and Healthy Control Subjects

TMS-Targeted Cortical Areas (Talairach Coordinates) and TMS-Evoked EEG Oscillation Parameters	Mean (SD)		F Score	P Value, Unpaired t Test
	Healthy Control Subjects	Patients With Schizophrenia		
Prefrontal cortex (−15, 55, 35)				
TMS-evoked oscillatory activity, ERSP, μV	107.5 (8.8)	91.8 (4.2)	57.1	<.001
TMS-evoked synchronization, ITC	10.9 (3.7)	6.5 (2.8)	9.5	.004
Natural frequency, Hz	31.0 (4.0)	21.5 (2.1)	108.9	<.001
Premotor cortex (−25, −10, 55)				
TMS-evoked oscillatory activity, ERSP, μV	142.3 (34.7)	108.0 (22.5)	16.4	<.001
TMS-evoked synchronization, ITC	16.0 (8.2)	11.2 (6.7)	5.9	.02
Natural frequency, Hz	26.5 (2.7)	20.2 (2.4)	49.1	<.001
Motor cortex (−25, −25, 55)				
TMS-evoked oscillatory activity, ERSP, μV	149.1 (34.4)	125.5 (26.0)	5.9	.02
TMS-evoked synchronization, ITC	19.3 (8.5)	16.0 (6.0)	2.1	.15
Natural frequency, Hz	21.8 (2.9)	19.2 (2.5)	6.3	.01
Parietal cortex (−5, −45, 50)				
TMS-evoked oscillatory activity, ERSP, μV	108.8 (15.9)	100.7 (20.6)	1.9	.18
TMS-evoked synchronization, ITC	24.1 (9.3)	23.9 (10.1)	2.1	.16
Natural frequency, Hz	19.9 (1.9)	18.7 (2.5)	2.5	.12

Abbreviations: EEG, electroencephalographic; ERSP, event-related spectral perturbation; ITC, intertrial coherence; TMS, transcranial magnetic stimulation.

stimuli delivered at 0.4 to 0.6 Hz according to international safety guidelines.[16] To ensure wakefulness during the TMS/HD-EEG sessions, subjects had their eyes open and fixated on a cross on a computer screen. We also recorded a session of waking, eyes-open, spontaneous EEG in each participant.

COGNITIVE TASKS

On a different day, a subset of patients with schizophrenia (n=15) underwent 2 computer-based cognitive tasks, the Penn Word Recognition Test and the Penn Facial Memory Test.[17] The Penn Word Recognition Test is lateralized to the left hemisphere (the hemisphere herein targeted by TMS) and particularly involves the prefrontal, language-related cortical areas.[18] The Penn Facial Memory Test, which targets right hemisphere areas[19] using faces, was performed to control for lateralization and to evaluate the specificity of the Penn Word Recognition Test findings.

DATA ANALYSIS

Data analysis was performed using Matlab software (MathWorks) and the public-licensed toolbox EEGLAB.[20] Data were from experiments specifically designed for this study and did not include recordings from our previous TMS/HD-EEG study.[11] The EEG signals were down sampled (from 1450 to 725 Hz), band passed (2-80 Hz), and average referenced. Trials containing activity from nonneural sources were automatically rejected if the electro-oculogram exceeded 70 μV (ocular activity) and/or the absolute power of EEG channel F8 in the fast beta range (>25 Hz) exceeded 0.9 μV^2, indicating activity of the frontotemporal muscles.[21]

Several TMS-evoked EEG oscillation parameters were analyzed in the time-frequency domain. The ITC was computed as a measure of synchronization, whereas event-related spectral perturbation (ERSP) was calculated to quantify amplitude modulation independent of phase.[20] To obtain ERSP for each TMS session, we calculated the power spectrum for every trial using wavelet decomposition (3.5 oscillation cycles) and computed the average power across trials. Then, ERSP was normalized by subtracting the mean baseline power. Significant ERSP was detected using a bootstrap method based on a surrogate data distribution randomly extracted from before the stimulus. Statistical significance was set at $P=.01$. Next, for each subject, the mean ITC and ERSP values averaged across all trials of a session were calculated for each channel between 8 and 50 Hz (1-Hz bin resolution). Finally, the main frequency (natural frequency) was computed as the frequency bin with the largest cumulated ERSP. The natural frequency differs from the peak frequency, which is usually calculated as the frequency with the largest activity at any time following a stimulus. A 20- to 300-millisecond time window was chosen to assess group differences in TMS-evoked EEG parameters, corresponding to the EEG activity significantly evoked by TMS, assessed with the bootstrap analysis. The first 20 milliseconds were excluded to avoid a stereotypical, broadband, early (0- to 20-millisecond) component occurring at each stimulation site. The ERSP, ITC, and natural frequency were calculated globally by averaging their values across all channels as well as locally by measuring them in the channel closest to the TMS coil. Because statistical comparisons across groups yielded similar results with global and local EEG oscillation parameters, local data are shown as they more closely reflect the activity of the TMS-targeted cortical areas. For spontaneous EEG analysis, data were band-pass filtered (2-80 Hz), bad channels were visually identified and rejected, and EEG signals were average referenced. After removal of segments contaminated by eye movements or muscle activity, power spectral density (Welch periodogram with 6-second epoch Hamming window) was calculated.

STATISTICAL ANALYSIS

Two-tailed bootstrap statistics were applied to ERSP and ITC values. Two-tailed unpaired *t* tests were used to establish statistical differences for ITC, ERSP, natural frequency, spontaneous EEG analysis, and clinical variables between the 2 study groups. For the natural frequency, group × region repeated-measures analyses of variance followed by post hoc Bonferroni-corrected *t* tests were computed to establish a progressive natural frequency increase from posterior to anterior areas in healthy subjects but not patients with schizophrenia. Pearson correlation analysis between medication doses, expressed in chlor-

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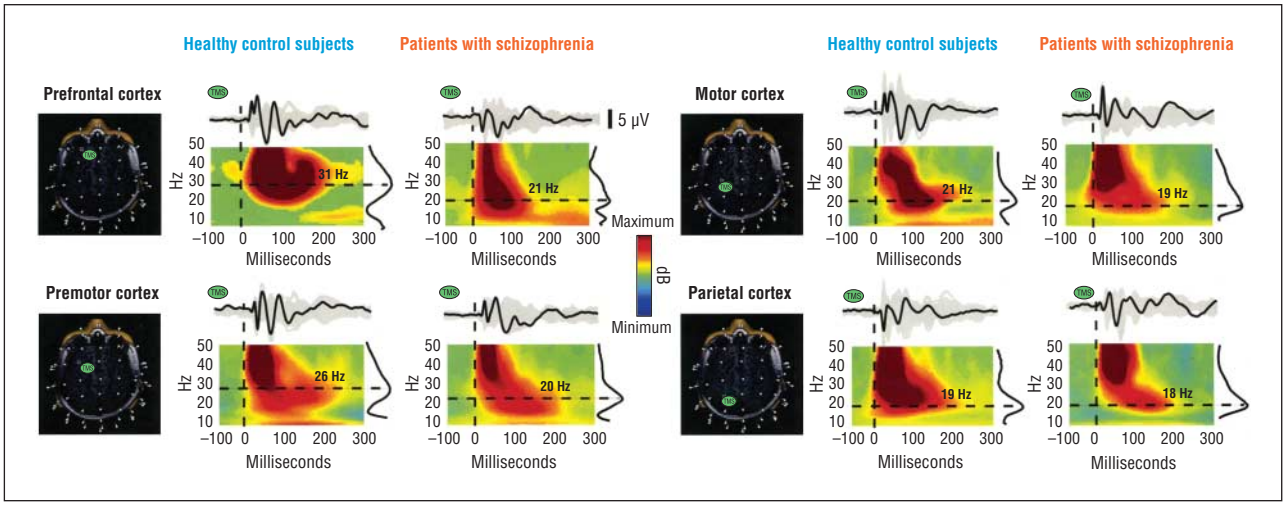

Figure 1. Patients with schizophrenia showed a reduction in several transcranial magnetic stimulation (TMS)–evoked fast oscillation parameters, including amplitude, duration, and frequency content in frontal cortical areas. The TMS was administered to 4 cortical areas (shown in the 3-dimensional individual magnetic resonance imaging reconstruction), and TMS-evoked electroencephalographic responses were collected for patients with schizophrenia and healthy control subjects (gray traces). The black traces reflect the responses at the electrodes closest to the TMS. Data are shown for a representative subject from each group. Event-related spectral perturbation plots show the TMS-related changes in amplitude and their duration, with dotted lines highlighting the frequency with the highest activity, the natural frequency, for each cortical area.

promazine equivalents,[22] and the natural frequency of the parietal, motor, premotor, and prefrontal areas were performed (eTable, http://www.archgenpsychiatry.com). Finally, the prefrontal natural frequency, the most defective EEG parameter in patients with schizophrenia, was correlated with PANSS scores as well as performance and reaction time in the Penn Word Recognition Test for patients with schizophrenia.

RESULTS

FRONTAL/PREFRONTAL EEG OSCILLATION DEFICITS IN SCHIZOPHRENIA

Figure 1 shows EEG responses after TMS of each area superimposed on butterfly plots, with gray traces corresponding to individual channels and black traces indicating the channel closest to the TMS (data are from a representative subject for each group, whose natural frequency closely matched the natural frequency group means displayed in **Figure 2**). Following an initial broadband response that occurred in each targeted cortical area, TMS evoked several fast (>13-Hz) EEG oscillations in both healthy subjects and patients with schizophrenia. However, whereas these oscillations were progressively faster in frequency from the parietal to the prefrontal cortex in healthy subjects, this posterior-anterior frequency increase was much more limited in patients with schizophrenia. Furthermore, the amplitude and synchronization of EEG oscillations in frontal/prefrontal locations were increasingly reduced in patients with schizophrenia compared with healthy subjects.

To quantify such differences, several TMS-evoked EEG oscillation parameters, including amplitude modulation (ERSP), synchronization (ITC), and main frequency, were calculated for each participant and compared between groups (Table 2, data for ERSP and ITC were cumulated between 8-50 Hz and 20-300 milliseconds, respectively, following TMS). The TMS-evoked EEG parameters were cumulated for 2 reasons: (1) to establish whether the total amplitude (ERSP) and synchronization (ITC) evoked by TMS were reduced in patients with schizophrenia compared with healthy control subjects in any of the 4 targeted cortical areas; and (2) to characterize the natural oscillatory frequency of these brain regions. The natural frequency is the main frequency at which a system oscillates and is best computed by cumulating the oscillatory activity after TMS and selecting the frequency showing the largest activity. Following TMS of the parietal cortex, no difference in EEG oscillation parameters was found across groups. By contrast, ERSP and the main frequency of EEG oscillations evoked by TMS of the motor cortex were significantly reduced in patients with schizophrenia compared with healthy subjects (Table 2). For the motor cortex, we also found that the motor threshold was not different between patients with schizophrenia (mean [SD], 61.7% [6.2%]) and healthy subjects (mean [SD], 60.4% [5.7%]). The TMS-evoked EEG oscillations of premotor cortex showed clear deficits in all parameters measured, including synchronization (ITC), in patients with schizophrenia (Table 2). Differences between patients with schizophrenia and healthy subjects were even more prominent after TMS of the prefrontal cortex, with EEG oscillations markedly smaller, less synchronous, and slower in frequency in patients with schizophrenia (Table 2).

SLOWED PREFRONTAL OSCILLATIONS IN SCHIZOPHRENIA

Because the natural frequency was the most altered TMS-evoked EEG oscillation parameter at the group level, we compared the individual natural frequency of patients with schizophrenia and healthy subjects for each cortical region stimulated. Whereas frequency values at the parietal cortex were largely overlapping between groups, patients

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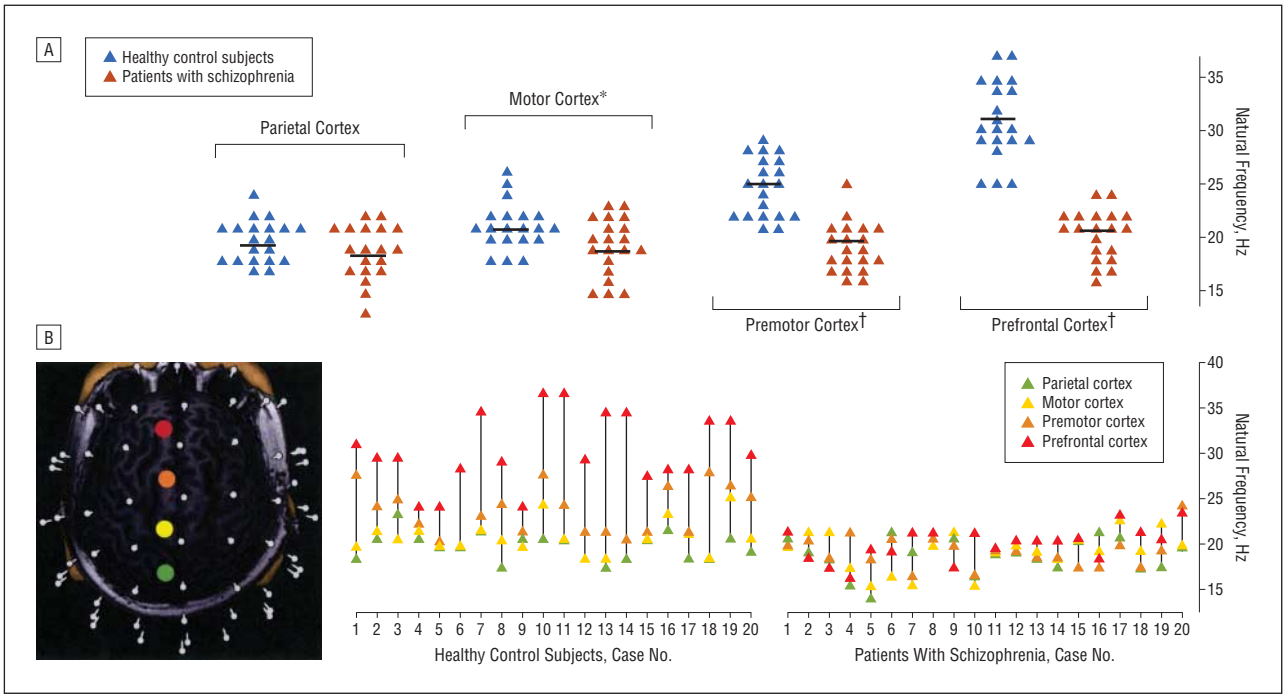

Figure 2. The frequency of transcranial magnetic stimulation–evoked prefrontal oscillations was the most sensitive parameter for identifying patients with schizophrenia and healthy control subjects. A, The individual natural frequency values of healthy control subjects and patients with schizophrenia are shown for 4 cortical areas. Horizontal lines indicate mean natural frequency values of each group for each cortical area. *$P<.05$; †$P<.001$. B, The natural frequency at these cortical areas, which are displayed in 3-dimensional magnetic resonance imaging, is shown for each study participant.

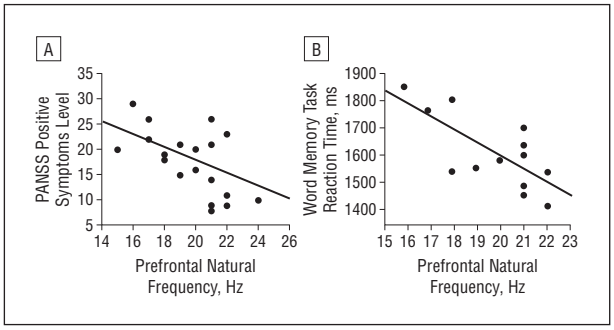

Figure 3. The frequency of prefrontal cortex oscillations was inversely related to the level of positive symptoms on the Positive and Negative Syndrome Scale (PANSS) (A) as well as to the reaction time of correct responses on a word memory task (B) in patients with schizophrenia.

with schizophrenia showed a progressive slowing in the natural frequency of the frontal cortical areas, which permitted an increasing separation from healthy control subjects. Group × region analyses of variance showed significant effects for group ($F=84.9$; $P<.001$), region ($F=38.7$; $P<.001$), and group × region interaction ($F=23.9$; $P<.001$). Post hoc Bonferroni-corrected t tests established that in healthy control subjects, the premotor natural frequency was faster than the motor frequency ($P<.001$) and the prefrontal natural frequency was significantly faster than the frequency of the other cortical areas ($P<.001$). By contrast, in patients with schizophrenia, there was no difference between the natural frequency of the 4 areas, suggesting a failure to show the parietal-prefrontal frequency increase of healthy comparison subjects (Figure 2B). Furthermore, the prefrontal natural frequency could distinguish each patient with schizophrenia from healthy subjects because the highest prefrontal natural frequency in patients with schizophrenia was 24 Hz, while the lowest value in control subjects was 25 Hz (Figure 2A). To assess sex effects, a factorial analysis of variance with natural frequency as a dependent variable and group and sex as categorical predictors was performed. This analysis showed that group was highly significant ($F=80.0$; $P<.001$), whereas sex failed to reach significance ($F=0.4$; $P=.52$) and showed no interaction with group ($F=2.5$; $P=.12$). Within-subject reproducibility of the prefrontal natural frequency was assessed in a subset of patients with schizophrenia (n=7) and healthy control subjects (n=11) and was found to be highly stable (±2 Hz, eFigure 1). To confirm that no outliers were driving group effects and correlations and to establish that individual prefrontal natural frequency values were within expected group-level ranges, we performed the Grubbs test.[23] No outliers in either the healthy group (highest Z score=1.74; critical Z score=2.73; $P>.05$) or the schizophrenia group (highest Z score=1.91; critical Z score=2.74; $P>.05$) were found.

PREFRONTAL NATURAL FREQUENCY CORRELATION ANALYSIS

We also performed correlation analysis between the prefrontal natural frequency and PANSS scores and found that the prefrontal natural frequency was inversely related to positive symptoms ($r=-0.55$; $P=.01$) (**Figure 3**A). Prefrontal natural frequency values showed the strongest inverse correlation with 2 subscores of PANSS positive symptoms, feeling of grandiosity (item P5; $r=-0.51$; $P=.02$) and delusions (item P1; $r=-0.62$; $P=.003$). By contrast, the prefrontal natural frequency did not correlate with medication doses in patients with schizophrenia (eTable).

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NO DEFICITS IN SPONTANEOUS EEG ACTIVITY IN SCHIZOPHRENIA

Topographic analysis of gamma-range (30- to 50-Hz) spontaneous EEG showed similar activity across groups throughout the scalp, including the prefrontal region (eFigure 2). Statistical comparison found no difference between patients with schizophrenia and healthy control subjects ($F_{1,38}=1.3$; $P=.35$). To investigate spontaneous gamma activity immediately preceding TMS, we averaged gamma activity in the 300 milliseconds before TMS of the prefrontal cortex in each subject and performed an unpaired *t* test between patients with schizophrenia and healthy individuals. No significant difference in gamma activity between groups was found (healthy subjects, mean=0.21 μV^2; patients with schizophrenia, mean=0.13 μV^2; $F_{1,38}=3.3$; $P=.08$).

PREFRONTAL NATURAL FREQUENCY AND COGNITIVE TASKS IN SCHIZOPHRENIA

To assess whether slowing of the prefrontal natural frequency affected some aspects of cognitive performance in schizophrenia, a subset of patients with schizophrenia completed 2 computer-based cognitive tasks, the Penn Word Recognition Test and the Penn Facial Memory Test. Overall performance and median reaction time were correlated with prefrontal natural frequency values in these patients. We found that while patients with schizophrenia did not significantly differ in the total number of correctly recognized words when compared with normative data from healthy comparison subjects (*Z* score=−0.14; *t* ratio=0.91; $P=.42$), their reaction time for correctly identified words was significantly slower (Z score=−1.10; *t* ratio=87.60; $P<.001$). Slowing of the prefrontal natural frequency in patients with schizophrenia, which did not correlate with their overall performance ($r=-0.11$; $P=.80$), was inversely related to their reaction time for correctly identified words ($r=-0.63$; $P=.02$) (Figure 3B). By contrast, no significant correlation between the prefrontal natural frequency and reaction time on the Penn Facial Memory Test was found ($r=-0.29$; $P=.30$).

COMMENT

We used TMS to directly perturb the posterior parietal, motor, premotor, and prefrontal regions and used HD-EEG to measure their oscillatory activity. We found a reduction in TMS-related amplitude (ERSP) and synchronization (ITC) of beta/gamma-band EEG oscillations recorded at frontal/prefrontal sites in patients with schizophrenia compared with healthy control subjects. Patients with schizophrenia also showed a slowing in the main oscillatory frequency, or natural frequency, of frontal/prefrontal oscillations. Each patient with schizophrenia had a slower prefrontal natural frequency than any healthy comparison subject, and this prefrontal slowing predicted the level of positive symptoms and reaction time in a word memory task.

Frontal beta/gamma-band deficits were recently reported in schizophrenia. Patients with schizophrenia had decreased beta synchrony and perceptual impairments in a study of long-range synchronization during face perception[24] and a reduction of beta-band power associated with auditory gating deficits.[25] Deficits in frontal fast synchrony and amplitude were shown by event-related studies, including oddball[9,26-28] and illusory square discrimination visual[29] paradigms, as well as by studies using cognitive probes[3,30] in patients with schizophrenia. A recent EEG study showed that during an N-back task, increased prefrontal gamma oscillations correlated with greater cognitive demand, and repetitive TMS could potentiate gamma oscillations in healthy subjects but not patients with schizophrenia.[31] Another EEG study using TMS to directly perturb a frontal area (premotor cortex) found that patients with schizophrenia had decreased frontal gamma amplitude (ERSP) and synchronization (ITC) compared with healthy comparison subjects.[11]

One aim of this study was to establish whether TMS-evoked EEG fast oscillation deficits were specific for frontal thalamocortical circuits in schizophrenia. Whereas no difference was found in evoked EEG oscillations after TMS of the parietal cortex between patients with schizophrenia and healthy subjects, the patients with schizophrenia had smaller evoked EEG oscillations following TMS of the motor area. Because there were no motor threshold differences across groups, these findings argue against differences in neuronal excitability between patients with schizophrenia and healthy subjects and likely reflect impairments in local cortical and thalamocortical circuits in schizophrenia.[32,33] Although some fast, gamma-range oscillations were observed right after TMS in the parietal and motor regions, the main oscillatory activity (ie, natural frequency) of these areas was in the low beta band. The TMS-evoked beta-range motor oscillation reduction in patients with schizophrenia is consistent with decreased beta-band sensorimotor synchronization during a self-paced button-press paradigm[34] as well as reduced contralateral sensorimotor beta oscillations during proprioceptive evoked potentials[35] found in patients with schizophrenia compared with healthy control subjects.

An important goal of this study was to establish whether deficits in prefrontal high beta/gamma oscillations, which were much smaller and less synchronous in patients with schizophrenia, were due to an intrinsic defect of underlying thalamocortical circuits. To achieve this goal, we capitalized on recent TMS/HD-EEG work showing the possibility of characterizing the intrinsic oscillatory frequency, or natural frequency, of human thalamocortical circuits. In this study, TMS consistently evoked α-band oscillations in the occipital cortex, low beta-range oscillations in the parietal cortex, and high beta/gamma oscillations in the premotor area in healthy control subjects.[12] Herein, we found that the prefrontal natural frequency was markedly defective in patients with schizophrenia, to the extent that there was no overlap between prefrontal frequency values across groups. A limitation of the present study was that the 2 groups were not sex matched (Table 1); however, sex differences are unlikely to account for these findings. Indeed, a factorial analysis of variance showed no sex effects on the prefrontal natural frequency differences between patients with schizophrenia and healthy subjects. Furthermore, the absence of overlap between patients with schizophrenia and

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healthy subjects suggests that regardless of sex, these patients were unable to generate prefrontal oscillations at the same frequency as healthy control subjects.

Recent imaging data suggested an implication of the prefrontal cortex in positive symptoms, especially delusions. A functional MRI study showed that reduced prefrontal-hippocampal connectivity correlated with higher PANSS positive symptoms in patients with schizophrenia,[36] while another functional MRI study reported that increased delusion severity in patients with schizophrenia was associated with decreased prefrontal activation during a reward task.[37] Herein, we found that the prefrontal natural frequency was inversely related to positive symptoms and that the strongest correlation was with delusion PANSS subscores in patients with schizophrenia. Recent modeling work demonstrated that reduced γ-aminobutyric acid (GABA)–ergic inhibition within prefrontal circuits increases vulnerability to psychosis,[38] whereas another modeling study showed that reductions in GABAergic activity resulted in reduced cortical fast oscillations.[39] Thus, a common mechanism underlying both the slowing of the prefrontal natural frequency and the increased severity of psychosis may be a decreased (GABAergic) inhibitory control on cortical excitatory neurons.

A defect of prefrontal circuits may also cause performance impairments in perceptual and cognitive tasks in schizophrenia.[40] For example, during an auditory oddball paradigm, patients with schizophrenia showed enhanced nonstimulus-related frontal EEG activity, which negatively correlated with performance in an N-back working memory task.[41] Another study using a cognitive control task found that patients with schizophrenia had reduced frontal gamma power compared with healthy control subjects, and gamma reduction was inversely correlated with task performance.[4] In a recent functional MRI study using a word memory task (Penn Word Recognition Test), patients with schizophrenia had reduced activation in the left prefrontal cortex and thalamus during the recognition phase, even when restricting blood oxygenation level–dependent analysis to correct responses.[18] Herein, the same task was used and the left prefrontal natural frequency slowing predicted an increased reaction time. Notably, no correlation was found with performance on the Penn Word Recognition Test, a word memory task implicating primarily right hemisphere areas, suggesting that the prefrontal natural frequency slowing provides a sensitive measure for deficits in lateralized cognitive functions. While the link between the natural frequency and memory needs to be established in future studies, a reduced ability to generate fast oscillations, reflected by the prefrontal natural frequency slowing, may be implicated in memory impairments; this was suggested by recent rat electrophysiological data showing that decreased prefrontal gamma-band oscillations, combined with reduced theta hippocampal activity and disrupted hippocampal-prefrontal coherence, were associated with worse performance in memory tasks.[42]

No difference in spontaneous prefrontal EEG activity between healthy subjects and patients with schizophrenia was found. This is likely related to the variability of spontaneous EEG oscillations. Resting-state oscillations in a given area may reflect local activity or may be driven by the activity of other regions or by sudden changes in the cognitive state. Thus, the intrinsic activity of a given area is best assessed by directly and selectively activating it (ie, with TMS) and by measuring its output (ie, prefrontal natural frequency).

Two possible mechanisms could be responsible for the prefrontal natural frequency slowing: (1) an intrinsic deficit of prefrontal cortical neurons, and (2) a defect in prefrontal thalamocortical circuitry. The GABAergic cortical interneurons can initiate and maintain fast oscillations, generating inhibitory postsynaptic potentials in excitatory pyramidal neurons. Inhibitory postsynaptic potentials enable the synchronization of large populations of pyramidal neurons, and their duration determines the main oscillatory frequency of these neurons.[43] Among GABAergic interneurons, fast-spiking cells expressing the calcium ion–binding protein parvalbumin are particularly important; recent in vivo experiments in mice demonstrated that inhibiting fast-spiking parvalbumin interneurons suppressed gamma oscillations, whereas driving these interneurons was sufficient to generate gamma-band rhythmicity.[44] Similarly, decreasing fast-spiking interneuron output in a computational model of a cortical area reduced power and synchronization of gamma oscillations.[45]

Deficits in GABAergic activity have been consistently reported in schizophrenia,[46] and genetic studies found that patients with schizophrenia had a reduction in the messenger RNA of glutamate decarboxylase 67, an enzyme involved in GABA synthesis, and in the density of GABA membrane transporter 1,[47] which was most prominent in parvalbumin-positive interneurons.[48] The presence of GABA deficits in schizophrenia is also supported by the observation that clozapine, regarded as the most effective antipsychotic, is associated with potentiation of cortical GABA activity[49] and by the improvement of psychosis with BL-1020, a GABA agonist, in patients with schizophrenia.[50] A GABA deficiency is also suggested by the beneficial effects of cortical stimulation techniques (eg, electroconvulsive therapy and repetitive TMS), which enhance GABA-mediated control on pyramidal neurons via cortical interneurons, in patients with schizophrenia.[51]

Furthermore, a recent TMS/HD-EEG study showed a decrease in GABA-mediated cortical inhibition in the dorsolateral prefrontal cortex of patients with schizophrenia compared with healthy control subjects.[52] A reduction in GABAergic interneurons was recently demonstrated beyond the prefrontal cortex in schizophrenia.[53] Additionally, gamma-band deficits were reported in sensory cortices using steady-state auditory[54] and visual[55] stimulation as well as visual probes evoking fast oscillations[56] in patients with schizophrenia. These findings are consistent with the idea that GABAergic deficits become functionally apparent when cortical areas oscillate at fast frequencies. We found that, of the regions tested, the prefrontal cortex (which intrinsically oscillates at the high beta/gamma range) was the most defective in patients with schizophrenia.

Besides cortical neurons, thalamic and thalamocortical neurons have been implicated in generating fast oscillations. Recent simultaneous EEG and functional MRI

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recordings in humans during a working memory task showed load-dependent effects on blood oxygenation level–dependent and EEG gamma-band activity in both the prefrontal cortex and the thalamus.[57] Furthermore, intracellular thalamic recordings combined with cortical local field potentials demonstrated that EEG gamma oscillations are associated with gamma-band oscillatory activity in both thalamic and cortical neurons.[58] In the thalamus, most inhibitory neurons are located within the thalamic reticular nucleus (TRN). The TRN consists entirely of GABAergic neurons, receives projections from corticothalamic and thalamocortical neurons, and sends efferents to all dorsal thalamus nuclei.[59] Intracellular and extracellular rat recordings showed that TRN neurons can intrinsically oscillate at 30 to 60 Hz and can be the gamma-band oscillation pacemakers during wakefulness.[60] The TRN is also the pacemaker of sleep spindles, a non–rapid eye movement sleep fast oscillation, and 2 recent studies found marked deficits in the spindle activity of patients with schizophrenia compared with healthy and psychiatric control subjects.[61,62] Thus, the TRN, which is strategically placed between the cortex and the thalamus, may be part of a defective cortico-TRN-thalamus circuitry underlying thalamocortical oscillation abnormalities in schizophrenia.[63]

Future studies are needed to address some of the questions left unanswered in this study. Patients with schizophrenia were medicated, which raises the question of whether the prefrontal natural frequency slowing was simply a medication effect. If so, one would expect a generalized, aspecific effect of antipsychotic medications on TMS-evoked EEG oscillations, which is inconsistent with the finding that the natural frequency of other cortical areas was unaffected (parietal cortex) or only partially reduced (motor cortex). Additionally, there was no correlation between medication doses and the prefrontal natural frequency of patients with schizophrenia, even after excluding the patients receiving first-generation antipsychotics. Furthermore, a recent study showed that both unmedicated patients with first-episode schizophrenia and medicated patients with schizophrenia had reduced task-related frontal gamma oscillations compared with healthy subjects, suggesting deficits in generating frontal fast oscillations in schizophrenia independent of medication status.[4]

Herein, we found that the prefrontal natural frequency slowing in schizophrenia was such that there was no overlap between patients with schizophrenia and healthy subjects. Future studies are needed to confirm this finding in larger groups of patients, including first-break individuals, as well as in first-degree relatives of probands with schizophrenia. This would help to establish the potential of these measures as biological markers[64] as well as endophenotypes[65] for schizophrenia. Furthermore, collecting and comparing EEG parameters (eg, TMS-evoked EEG oscillations, non–rapid eye movement sleep spindles) with several clinical and cognitive measures in the same patient population may help reveal which brain activity measures predict impaired cognitive performances and clinical symptoms in schizophrenia.[66] As a first step in that direction, the findings reported here of a correlation between reduced prefrontal natural frequency, increased reaction time in a word memory task, and higher scores of positive symptoms in patients with schizophrenia point to a common deficit of the underlying prefrontal cortical/thalamocortical circuitry.

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