ORIGINAL ARTICLE

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Probing Thalamic Integrity in Schizophrenia Using Concurrent Transcranial Magnetic Stimulation and Functional Magnetic Resonance Imaging

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Context: Schizophrenia is a devastating illness with an indeterminate pathophysiology. Several lines of evidence implicate dysfunction in the thalamus, a key node in the distributed neural networks underlying perception, emotion, and cognition. Existing evidence of aberrant thalamic function is based on indirect measures of thalamic activity, but dysfunction has not yet been demonstrated with a causal method.

Objective: To test the hypothesis that direct physiological stimulation of the cortex will produce an abnormal thalamic response in individuals with schizophrenia.

Design: We stimulated the precentral gyrus with single-pulse transcranial magnetic stimulation (spTMS) and measured the response to this pulse in synaptically connected regions (thalamus, medial superior frontal cortex, insula) using concurrent functional magnetic resonance imaging. The mean hemodynamic response from these regions was fit with the sum of 2 gamma functions, and response parameters were compared across groups.

Setting: Academic research laboratory.

Participants: Patients with schizophrenia and sex- and age-matched psychiatrically healthy subjects were recruited from the community.

Main Outcome Measure: Peak amplitude of the thalamic hemodynamic response to spTMS of the precentral gyrus.

Results: The spTMS-evoked responses did not differ between groups at the cortical stimulation site. Compared with healthy subjects, patients with schizophrenia showed a reduced response to spTMS in the thalamus ($P = 1.86 \times 10^{-9}$) and medial superior frontal cortex ($P = .02$). Similar results were observed in the insula. Sham TMS indicated that these results could not be attributed to indirect effects of TMS coil discharge. Functional connectivity analyses revealed weaker thalamus–medial superior frontal cortex and thalamus-insula connectivity in patients with schizophrenia compared with control subjects.

Conclusions: Individuals with schizophrenia showed reduced thalamic activation in response to direct perturbation delivered to the cortex. These results extend prior work implicating the thalamus in the pathophysiology of schizophrenia and suggest that the thalamus contributes to the patterns of aberrant connectivity characteristic of this disease.

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SCHIZOPHRENIA IS A DEVASTATING mental illness that has a significant impact on family, caregivers, society, and patients.[1-3] More than 2.4 million Americans are diagnosed as having schizophrenia,[4] and mortality rates are 2 to 3 times greater for these patients compared with the population as a whole.[5,6] Although research has focused heavily on identifying diagnostic tools[7] and treatments[8] for the illness, schizophrenia is currently diagnosed based on clinical criteria,[9] treatments are often ineffective,[10] and the pathophysiology of the disease remains elusive. The work presented here builds on numerous prior studies that have implicated dysfunction of the thalamus in schizophrenia. We review the theoretical and empirical basis for this hypothesis of thalamic dysfunction in schizophrenia and conclude that much of the extant evidence is either indirect or subject to significant inferential limitations. For instance, some studies rely on cortical differences or effects measured at the scalp to draw inferences about thalamic dysfunction. Others infer functional differ-

ences on the basis of structural measures or rely on the assumption that patient and control groups perform behavioral tasks in a comparable manner. We designed our experiment to circumvent these limitations, using single-pulse transcranial magnetic stimulation (spTMS) to directly stimulate the cortex and concurrent functional magnetic resonance imaging (fMRI) to measure the resulting thalamic response.

Three lines of evidence suggest that schizophrenia is associated with thalamic dysfunction. First, aberrant scalp-recorded electrophysiological indices of sensory gating in schizophrenia have been interpreted as evidence for thalamic dysfunction, given nonhuman research confirming the critical role of the thalamus in conceptually similar processes.[11-15] Sensory gating deficits in schizophrenia have been demonstrated using P50 prepulse inhibition,[16,17] a P300 auditory oddball paradigm,[18] and mismatch negativity tasks.[19-21] All of these paradigms have been interpreted as requiring thalamically mediated filtering of novel or salient stimuli. On this basis, some have suggested that hallucinations are a result of impaired thalamic filtering of salient and external speech from nonsalient and internal speech.[22,23]

A second line of evidence comes from overnight electroencephalographic studies demonstrating sleep spindle deficits in individuals with schizophrenia. Sleep spindles are waxing and waning 12- to 16-Hz oscillations initiated by the thalamic reticular nucleus (TRN) and regulated by thalamoreticular and thalamocortical circuits.[24,25] Individuals with schizophrenia display fewer and smaller sleep spindles. These metrics distinguish patients from healthy control subjects, medicated control subjects, and individuals with depression with high sensitivity and specificity.[26-28]

A third line of evidence implicating the thalamus in schizophrenia comes from studies that directly measured the thalamus using structural and functional neuroimaging techniques. Structural imaging studies have consistently identified decreases in thalamic gray matter[29-31] and aberrant thalamic morphology[32,33] in individuals with schizophrenia. In parallel, functional imaging studies have consistently found abnormal thalamic activation during sensory gating,[32,33] working memory,[34] and other executive function[35-40] tasks.

Although these studies have contributed to an important model of the pathophysiology of schizophrenia, most are subject to 1 of 3 key inferential limitations. One limitation is that studies using scalp-recorded electrophysiology, as in studies of sensory gating and sleep, do not measure thalamic activity directly. A second is that structural imaging studies cannot address thalamic physiology and are therefore unable to directly test hypotheses of thalamic dysfunction. A third is that most studies using fMRI measure thalamic activity in the context of task performance and are therefore susceptible to detecting group differences in physiology that are mediated by performance differences (eg, attention, compliance, comprehension, motivation, strategy) rather than differences in underlying disease-related neurobiology.[36-38]

The aim of our study was to circumvent these limitations and more directly test the hypothesis that the thalamus functions abnormally in schizophrenia. We used spTMS to present a direct physiological challenge to the cortex while we simultaneously measured the transynaptic response to this challenge in the thalamus with fMRI. Transcranial magnetic stimulation uses electromagnetic induction to noninvasively produce weak currents in the tissue underlying the TMS coil.[39] In addition to affecting the tissue that experiences the magnetic flux directly, depolarization at the stimulation site propagates to distal regions via synaptic transmission or spread of neural impulses.[40,41] Whereas repetitive TMS is thought to create a transient "virtual lesion" by overwhelming a brain region with noise[42] or otherwise altering ongoing neural functioning,[43,44] spTMS transiently excites discrete cortical patches without producing prolonged changes in cortical excitability or function. The use of spTMS permits concurrent measurement of both the local response and the response in distal regions functionally connected to the stimulation site.[41,45,46] In our study, the cortical and thalamic responses to spTMS were measured using blood oxygen level–dependent fMRI.[47] Although concurrent TMS-fMRI has been used to evaluate brain function in healthy individuals[48,49] and a number of commentators have highlighted the potential benefits of using this technique to probe the neurobiology of schizophrenia,[50,51] to our knowledge it has never before been applied to the study of any psychiatric illness.

Here, spTMS was delivered to the precentral gyrus and the resulting hemodynamic response was parameterized (amplitude, peak latency, and width) in 4 regions of interest (ROIs). Hypothesis testing focused on group differences in peak amplitude in the thalamus. Differences in the hemodynamic response were also assessed in the cortex beneath the TMS coil (precentral gyrus), the medial superior frontal gyrus (mSFG), and the insula. Exploratory analyses were used to characterize group differences in the latter 2 cortical ROIs, and measures of functional connectivity were computed. Results were compared with sham TMS. A button-pressing (BP) task was also assessed to confirm that spTMS-evoked responses were qualitatively similar to those obtained with a standard motor task. We hypothesized and demonstrated that patients with schizophrenia show a reduced thalamic response to spTMS.

METHODS

Procedures were approved by the University of Wisconsin–Madison Health Sciences Institutional Review Board. Written informed consent was obtained from all subjects.

SUBJECTS

Fourteen healthy subjects and 14 subjects with schizophrenia, recruited from local mental health care providers through newspaper and Internet advertisements and by word of mouth, participated in the study (**Table 1**). A psychiatrist interviewed all subjects to obtain psychiatric and medical histories and to exclude (healthy control subjects) or confirm (patients with schizophrenia) diagnoses using *DSM-IV-TR* criteria[9] (eAppendix, http://www.archgenpsychiatry.com). The Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Patient Edition[52] was also administered. Symptom severity was evaluated using the Positive and Negative Syndrome Scale.[53]

Table 1. Demographic and Clinical Characteristics of Healthy Control Subjects and Patients With Schizophrenia

Characteristic	Healthy Control Subjects (n = 14)	Patients With Schizophrenia (n = 14)	Analysis[a]
Age, mean (SD) [range], y	34.00 (8.04) [20-45]	32.93 (7.53) [25-48]	.72
Male/female, No.	10/4	10/4	
Education starting with high school, mean (SD), y	6.00 (2.51)	5.21 (2.12)	.38
Positive and Negative Syndrome Scale score, mean (SD)			
Positive	. . .	15.57 (6.03)	
Negative	. . .	20.71 (5.98)	
General	. . .	33.79 (10.45)	
Total	. . .	70.07 (17.66)	

Abbreviation: ellipses, not applicable.
[a]From *t* test.

Patients were diagnosed as having the following subtypes: paranoid (n=11), residual (n=1), catatonic (n=1), or undifferentiated (n=1). They were receiving second-generation (n=10), first- and second-generation (n=2), or first-generation (n=2) antipsychotic medications. All were outpatients with a stable chronic illness (mean [SD], 11 [7] years).

DESIGN OVERVIEW

The study consisted of 2 sessions occurring on separate days. During the first session, structural MRIs required for the subsequent spTMS-fMRI session were collected; data for the first session for some subjects were obtained from a prior study. The second session featured 2 challenges. The first was spTMS to the precentral gyrus of the left hemisphere. The second was a BP task known to produce a well-characterized hemodynamic response[54] (11 subjects performed this task during the first session).

Four criteria led us to select the precentral gyrus as the spTMS target. First, to ensure that spTMS-induced input to thalamus would be comparable across groups, we required a target that is not dysfunctional in schizophrenia. Thus, we ruled out the prefrontal cortex, for example.[55,56] Second, we required a target easily accessible in the scanner and not covered in musculature,[57] ruling out the occipital and temporal lobes. Third, we preferred a target that has a well-characterized hemodynamic response, that has been studied in prior TMS-fMRI research, and whose activity is associated with robust thalamic activity.[46,58] Fourth, given the sleep spindle abnormality described earlier,[26,59] we preferred a target with robust projections to the TRN.[60] The precentral gyrus satisfied all of these criteria.

Session 1: Structural MRI Data Acquisition

During the first session, T1-weighted high-resolution structural images (echo time [TE] = 3.2 milliseconds; repetition time [TR] = 8.2 milliseconds; field of view [FOV] = 25.6 cm; matrix = 256 × 256; 156 × 1.0-mm slices; no inversion recovery) were collected using a 3-T General Electric Discovery 750 MRI scanner. Single-subject data were transferred to a Navigated Brain Stimulation (frameless stereotaxy) system (Nexstim), and the TMS target (left precentral gyrus in the vicinity of the primary hand representation [knob][61]) was identified.

Session 2: spTMS Targeting and fMRI Acquisition

Session 2 included (1) coregistering the subject's head with the high-resolution T1 image to determine TMS positioning and (2) fMRI scanning. The order of functional scanning was as follows: spTMS to the precentral gyrus, BP task (if not obtained during the first session), spTMS to another TMS target (data not shown), and sham TMS (eAppendix). Each time the TMS coil was relocated, the subject was repositioned in the scanner. Following each scan with spTMS, a medium-resolution structural scan was obtained. All MRI sessions occurred at the same time of day (early afternoon).

spTMS Targeting. The Navigated Brain Stimulation system was used to coregister each subject to his or her own T1 (eFigure 1 and eAppendix). Stimulation intensity was determined by delivering spTMS at varying intensities (using a staircasing procedure[62]) to the hand area of the precentral gyrus until an intensity that evoked a contralateral motor response to 5 of 10 pulses was reached. The spTMS was delivered using a 70-mm figure-8 coil and biphasic stimulator (Magstim Rapid 2). To avoid evoking motor responses in the scanner, we used the Navigated Brain Stimulation system to move the coil along the precentral gyrus until a location that did not evoke a motor response was identified. Because the Navigated Brain Stimulation system is not MRI compatible, the exact position of the TMS coil was traced onto a cap worn by the subject, allowing stimulation to be delivered to the same location using an MRI-compatible TMS coil in the scanner. The subject was then escorted to the scanner.

fMRI Acquisition. To minimize startle from the click associated with the TMS coil, subjects were fitted with Avotec pneumatic headphones through which white noise was played during the session. Volume was titrated to the maximum level that the subject could comfortably tolerate. Foam padding was used to minimize movement. An MRI-compatible TMS coil (Magstim and Jali Medical) was attached to a custom multijointed mount (eFigure 1 and eAppendix). An 8-foot radiofrequency-shielded cable, passed through a waveguide in the penetration panel, connected the TMS coil in the scanner to the stimulator in the control room.

The TMS coil was aligned to the coil tracing on the subject's cap. Single pulses were delivered to confirm that movements were not evoked. Subjects were instructed to remain calm, still, and awake with open eyes.

The first scan was a localizer image, followed by a higher-order shim (TE = 7.0 milliseconds; TR = 1558 milliseconds; FOV = 24 cm; slice thickness = 5.8 mm) and field map (TE = 7 and 10 milliseconds; TR = 710 milliseconds; FOV = 20 cm; matrix = 256 × 256; 25 × 1.0-mm slices). This was followed by two 20-pulse runs of spTMS to the precentral gyrus (110% motor threshold; intertrial interval = 16-24 seconds) and one 20-pulse run of the BP task. To minimize TMS artifacts, the pulse sequence for these echo-planar images (TR = 2000 milliseconds; TE = 25 milliseconds; FOV = 22.4 cm; matrix = 64 × 64;

35 × 3.0-mm slices [0.6-mm gap]; flip angle = 60°) was modified such that image acquisition occurred during the first 1770 milliseconds of the TR, thereby leaving a 230-millisecond silent gap during which spTMS could be delivered (eFigure 2). The same pulse sequence was used for the BP task, during which subjects were instructed to press a button with their right thumb as firmly and as quickly as possible following a 500-millisecond tone (Current Designs). Stimuli were controlled by E-Prime (Psychology Software Tools) and transistor-transistor logic pulses generated by the scanner. Finally, a medium-resolution structural scan (TR = 4.3 milliseconds; TE = 1.22 milliseconds; FOV = 28 cm; matrix = 256 × 256; 60 × 2.6-mm slices) was collected.

The subject was then slid out of the scanner and the TMS coil was configured for sham stimulation. The procedure was repeated with 2 runs of sham TMS replacing spTMS (for details of the sham TMS procedure, see eAppendix). One subject in each group discontinued participation in the experiment prior to collection of sham TMS data.

DATA PREPROCESSING

Except where otherwise noted, processing used AFNI (http://afni.nimh.nih.gov)[63] and in-house software. Functional images were first reconstructed on the scanner. Images were corrected for slice time, motion, and field map using FSL software (http://www.fmrib.ox.ac.uk/fsl).[64] Data were masked to exclude extracerebral voxels and converted to percent signal change. Functional images were aligned to the high-resolution T1 using the transformation matrix generated by aligning the medium- to the high-resolution T1 and then applying the transformation matrix to the functional data (6 *df*, least squares, sinc interpolation; resampled to 3 × 3 × 3.6 mm).

For each subject, the hemodynamic response was modeled using a generalized least-squares fit with restricted maximum likelihood estimation of temporal autocorrelation. Hemodynamic responses were modeled using a set of triangular (tent) functions (9 tents; 0-16 seconds). Similar to other basis functions (eg, finite impulse responses), this allowed the amplitude, peak latency, and width of the hemodynamic response to vary.

ANALYSIS

The aim of this investigation was to test whether individuals with schizophrenia show an attenuated thalamic response to cortical spTMS. To accomplish this, we used an a priori ROI-based strategy. This approach has 2 advantages. First, statistical power is maximized by eliminating the need to correct for thousands of voxelwise comparisons. Second, this strategy circumvents the assumption that the thalamus is anatomically similar in patients and control subjects. The ROIs were prescribed in the axial plane on the high-resolution T1, referring to a human brain atlas[65] as needed (eTable 1 and eAppendix).

In addition to interrogating the stimulation site and the thalamus, we analyzed 2 other regions. The mSFG was selected for exploratory analyses after visual inspection of activation maps from the first 8 subjects enrolled in the study revealed that it was consistently and robustly activated by spTMS. When these analyses revealed abnormal thalamocortical coupling in schizophrenia, we assessed the generality of this finding by interrogating the insula, for which thalamic dysconnectivity in schizophrenia was recently reported.[66] Importantly, for each subject, the nearest border of the mSFG and insula ROIs was always located several centimeters from the site targeted for spTMS. Because direct electromagnetic induction is limited to an area of approximately 2 cm^2 and a depth of 2 cm,[67,68] the responses observed in these regions (and the thalamus) were necessarily due to synaptic transmission.

For each ROI, a mask was created containing the upper fifth percentile of voxels responsive to spTMS (determined using the *t* statistic at the peak of each individual's hemodynamic response [4-6 seconds]). The hemodynamic response from these voxels was parameterized using the sum of 2 gamma functions (in units of percent signal change). The gamma functions were upsampled from 2000-millisecond (ie, the original sampling rate) to 10-millisecond resolution.[69] This fit enabled us to extract model parameters corresponding to the amplitude, peak latency, and overall width (at approximately the full width at half maximum) of the hemodynamic response and then to compare them across groups.

For spTMS and sham TMS conditions, 1 of 2 runs was analyzed. Although a single 20-trial run is sufficient to produce a BP-evoked hemodynamic response,[54] the technical challenges inherent in measuring the spTMS-evoked response with fMRI led us to collect a second spTMS run as a backup. For the analyses reported here, we selected the run in which the *t* statistic (corresponding to the greatest difference from baseline) was most similar to that of the BP run (see eAppendix for details about run selection and results from analyses of unselected runs). To control for nonspecific TMS effects, thalamic voxels responsive to spTMS were also compared with sham TMS.

When analyses of the spTMS-evoked responses in the mSFG and insula revealed group differences in amplitude in these regions, we assessed group differences in functional connectivity among ROIs. Specifically, time series were averaged across the upper fifth percentile of voxels within each ROI for each subject, demeaned, correlated, and then *Z* transformed using the Fisher technique.

HYPOTHESIS TESTING

Between-groups analyses of variance, *t* tests, Pearson correlations, and discriminant analyses were performed with SPSS Statistics version 20.0.0 software (SPSS Inc). Gamma fit parameters were also assessed with nonparametric statistics, which yielded similar conclusions (not reported). Owing to nonnormality of the connectivity metric, coefficients were rank transformed prior to testing.[70,71] Hemodynamic response curves and their associated 95% CIs (computed using group means and standard errors at each time point) were plotted using in-house code written for R software (http://www.r-project.org). Effect size is reported as partial η^2. The spTMS and BP task were not formally compared because we did not have theoretically motivated hypotheses involving this comparison.

RESULTS

CORTICAL RESPONSE TO spTMS, BUT NOT BP TASK, IS SIMILAR ACROSS GROUPS

The spTMS-evoked response did not differ between groups in the precentral gyrus ($F_{1,26} = 0.52$; $P = .48$; $\eta^2 = 0.02$). However, during the BP task, patients with schizophrenia showed a wider hemodynamic response ($F_{1,26} = 5.86$; $P = .02$; $\eta^2 = 0.18$) (**Figure 1**). There were no group differences in BP reaction time ($F_{1,26} = 2.05$; $P = .16$; $\eta^2 = 0.07$).

THALAMIC RESPONSES TO spTMS AND BP TASK ARE ABNORMAL IN SCHIZOPHRENIA

In the spTMS condition, individuals with schizophrenia showed a smaller ($F_{1,26} = 80.79$; $P = 1.86 \times 10^{-9}$; $\eta^2 = 0.76$) and earlier peaking ($F_{1,26} = 4.39$; $P = .05$; $\eta^2 = 0.14$) thalamic response. Indeed, every patient showed a peak that

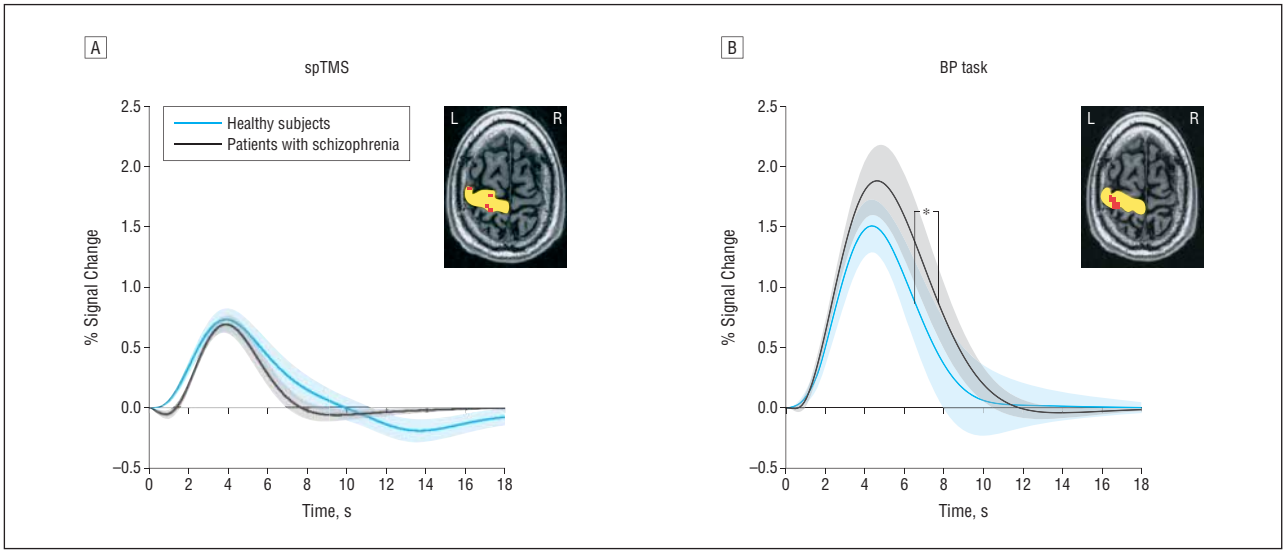

Figure 1. Group-averaged cortical response to single-pulse transcranial magnetic stimulation (spTMS) in the cortical region underlying the TMS coil (precentral gyrus) (A) and to a button-pressing (BP) task in the precentral gyrus (B) (n=14 in each group). Shaded areas indicate 95% CIs. *$P<.05$. Insets, Single-subject representation of the region of interest (yellow) and the voxels most responsive to the condition (red). L indicates left; R, right.

was numerically smaller than the least responsive member of the control group (**Figure 2**C) (range of percent signal change, 0.26%-0.80% for patients vs 0.88%-1.67% for healthy subjects). A formal discriminant analysis indicated that this measure did an excellent job classifying members of the 2 groups ($\chi^2=36.0$; $P=1.95\times10^{-9}$; leave-one-out cross-validation: sensitivity=85.7%; specificity=100.0%; overall classification accuracy=92.9%). Peripheral consequences of spTMS stimulation could not account for this effect because, compared with spTMS, sham TMS produced a nonexistent response (patients: $F_{1,12}=16.33$; $P=.002$; $\eta^2=0.58$; healthy subjects: $F_{1,12}=135.50$; $P=6.8\times10^{-8}$; $\eta^2=0.92$) that did not differ between groups ($F_{1,24}=3.0\times10^{-5}$; $P>.99$; $\eta^2=1.0\times10^{-6}$) (Figure 2). The BP task showed a similar, albeit weaker, pattern ($F_{1,26}=10.69$; $P=.003$; $\eta^2=0.29$) (Figure 2).

mSFG AND INSULA RESPONSES TO PRECENTRAL GYRUS spTMS ARE DECREASED IN SCHIZOPHRENIA

The spTMS-evoked response was smaller in magnitude in the mSFG in patients with schizophrenia compared with healthy control subjects ($F_{1,26}=6.56$; $P=.02$; $\eta^2=0.20$) (**Figure 3**). To explore possible factors underlying this difference, we assessed functional connectivity between the precentral gyrus and mSFG, between the mSFG and thalamus, and between the precentral gyrus and thalamus (using time-series correlations). These analyses found no group differences in precentral gyrus–mSFG connectivity ($F_{1,26}=0.47$; $P=.31$; $\eta^2=0.02$) or in precentral gyrus–thalamus connectivity ($F_{1,26}=0.02$; $P=.61$; $\eta^2=0.001$) but did reveal that patients with schizophrenia had reduced coupling between the thalamus and mSFG relative to healthy control subjects ($F_{1,26}=32.00$; $P=6.0\times10^{-5}$; $\eta^2=0.55$) (**Table 2**). Importantly, the lack of a group difference in coupling between the precentral gyrus and mSFG was not simply a function of low overall connectivity between these regions; actual magnitudes of the correlations reflected a relatively high level of functional connectivity in both groups (Table 2).

Variation in thalamocortical coupling also predicted the magnitude of the spTMS-evoked mSFG response. Across groups, subjects with lower thalamus-mSFG coupling showed a smaller evoked response in the mSFG ($\rho_{26}=0.37$; $P=.05$). Results for the insula were complementary to those for the mSFG (eFigure 3, eTable 2, and eAppendix).

CONTROL ANALYSES

Disease chronicity and medication dosage, assessed using chlorpromazine equivalents,[72] did not predict any of the brain measures (all $P>.13$). Across groups, variation in years of formal education did not predict any brain measure (all $P>.15$). Likewise, accounting for variation in education did not substantively alter the significance of any group difference. Because the majority of the patients with schizophrenia (n=11) were diagnosed as having paranoid schizophrenia and the remaining 3 subjects were diagnosed as having residual, undifferentiated, or catatonic schizophrenia, it was not possible to meaningfully assess the effect of subtype. Nevertheless, analyses performed with these 3 individuals omitted did not alter any of our conclusions.

THALAMIC DEFICITS AND SYMPTOM SEVERITY

There was a trend for patients with smaller thalamic responses to spTMS to show more severe positive symptoms on the Positive and Negative Syndrome Scale ($r_{12}=-0.49$; $P=.07$). Relationships with negative symptoms were not significant ($r_{12}=-0.17$; $P=.57$).

COMMENT

Schizophrenia is a severe mental illness whose neurobiology remains unclear.[1-3] There is considerable circum-

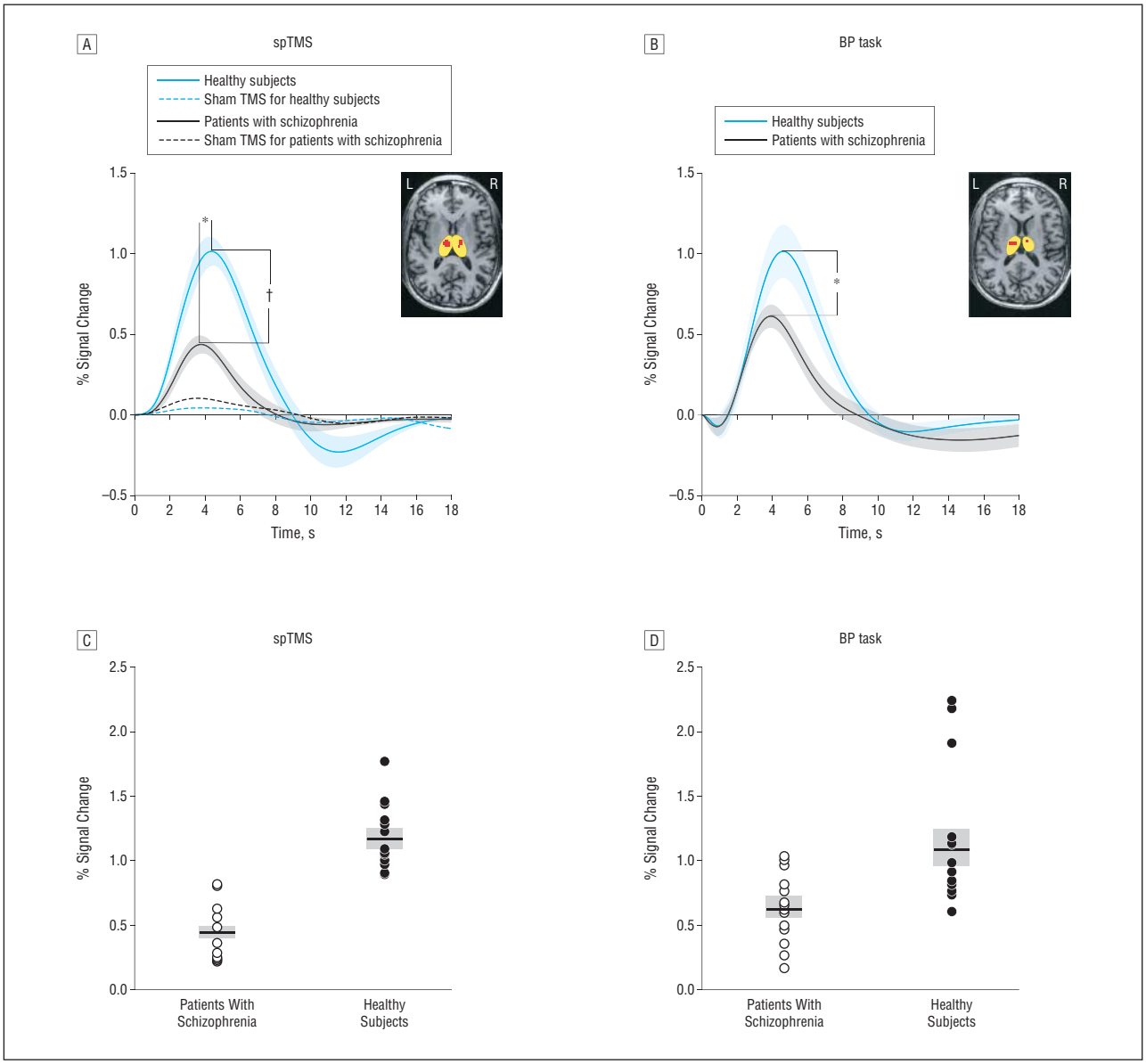

Figure 2. Group-averaged response to single-pulse transcranial magnetic stimulation (spTMS) (A) and to a button-pressing (BP) task (B) in the thalamus (n=14 in each group) as well as the sham TMS response in the same voxels (n=13 in each group). Shaded areas indicate 95% CIs. *$P<.05$; †$P=1.86\times10^{-9}$. Insets, Single-subject representation of the region of interest (yellow) and the voxels most responsive to the condition (red). L indicates left; R, right. Dot plots illustrate single-subject peak percent signal change (extracted 3-6.5 seconds following spTMS delivery) in response to spTMS (C) and the BP task (D) with the group means (horizontal lines) and SEMs (gray boxes) indicated. Because peak latency varied across subjects, the group means shown in C and D necessarily differ from the maxima of the average hemodynamic response function waveforms depicted in A and B. C and D represent data used for hypothesis testing.

stantial evidence of a thalamic abnormality in schizophrenia as assessed structurally[29,30] and functionally.[32,33] Our results strengthen this hypothesis of thalamic dysfunction in schizophrenia with a procedure that supports causal inference: subjects with schizophrenia evinced a smaller spTMS-evoked response in the thalamus compared with healthy control subjects. Analysis of a sham stimulation condition indicated that these effects could not be attributed to secondary consequences of spTMS. Additionally, because no group differences were found in response to spTMS in the precentral gyrus, the results likely reflect local deficits in thalamic physiology, not downstream consequences of deficits in cortical function.

ABNORMAL THALAMIC FUNCTIONING IN SCHIZOPHRENIA IS CONFIRMED WITH spTMS-fMRI

The average thalamic spTMS-evoked response in patients with schizophrenia was less than half the magnitude of the average response in healthy subjects. Although this measure identified individuals from the 2 groups with 100% specificity, additional research is needed to determine whether the groups are better characterized as falling into 1 of 2 clusters or as falling along a continuum on which patients with schizophrenia tend to have lower values. In terms of pathophysiology, the difference might be due to 1 of 3 factors: (1) a physiological abnormality in the stimu-

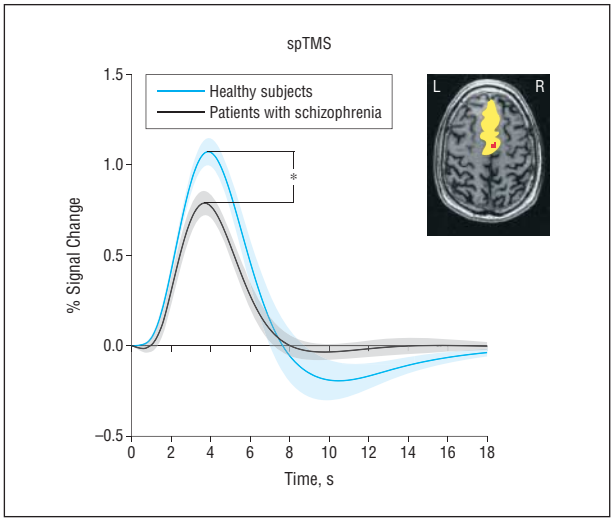

Figure 3. Group-averaged medial superior frontal gyrus response to single-pulse transcranial magnetic stimulation (spTMS) of the precentral gyrus (n=14 in each group). Shaded areas indicate 95% CIs. *$P<.05$. Inset, Single-subject representation of the region of interest (yellow) and the voxels most responsive to the condition (red). L indicates left; R, right.

Table 2. Group Mean Correlation Coefficient Between ROI Time Series

	Mean Correlation Coefficient, *r*	
ROI	Precentral Gyrus[a]	Thalamus[b]
Precentral gyrus		
Healthy control subjects	. . .	.35
Patients with schizophrenia	. . .	.38
mSFG		
Healthy control subjects	.49	.58
Patients with schizophrenia	.43	.35

Abbreviations: mSFG, medial superior frontal gyrus; ROI, region of interest; ellipses, not applicable.

[a] For the mSFG, $P = .31$ between healthy control subjects and patients with schizophrenia.

[b] For the precentral gyrus, $P = .61$ between healthy control subjects and patients with schizophrenia; for the mSFG, $P = 6.0 \times 10^{-5}$ between healthy control subjects and patients with schizophrenia.

lated cortical tissue, (2) deficient corticothalamic signal propagation, or (3) a physiological abnormality in the thalamus. The first possibility is ruled out by the fact that the response in cortical tissue underlying spTMS did not differ across groups. The second seems unlikely because the connectivity between the thalamus and precentral gyrus, that is, the degree of corticothalamic coupling, did not differ across groups. The most likely interpretation, therefore, is that our results reflect aberrant functioning of the thalamus itself, a claim consistent with evidence of structural abnormalities[29-31,73,74] in the thalamus in subjects with schizophrenia.

mSFG AND INSULA SHOW DECREASED spTMS-EVOKED RESPONSE IN SCHIZOPHRENIA

Group differences in spTMS-evoked responses were also observed in the mSFG and insula, cortical regions distal to the site of spTMS delivery. Such findings could be attributed to (1) a functional deficit in the mSFG or insula, (2) a deficit in the region of stimulation (precentral gyrus) or its coupling with the mSFG or insula, or (3) an abnormality in a third area that is connected to both the precentral gyrus and the mSFG or insula (eg, the thalamus) or the coupling with this third area. Again, the results of the functional connectivity analysis support the third possibility, revealing reduced coupling between the thalamus and mSFG and the thalamus and insula in patients with schizophrenia but no difference in the degree of coupling between the precentral gyrus and these regions. (Note that in healthy control subjects, coupling between the mSFG and thalamus was significantly stronger than coupling between the precentral gyrus and thalamus [eAppendix]. Although this specific pattern does not alter the reasoning behind our interpretation of the group difference in overall patterns of functional connectivity, it is an intriguing observation that may merit future investigation.) Further consistent with the third scenario, when data from the groups were combined, the strength of the thalamus-mSFG coupling predicted the magnitude of the TMS-evoked responses in the mSFG and, likewise, the strength of the thalamus-insula coupling predicted the magnitude of the TMS-evoked responses in the insula. Taken together, these observations strongly suggest that the group difference in the magnitude of the mSFG and insula responses to spTMS reflects deficits centered on the thalamus or thalamocortical circuitry rather than local cortical deficits. Thus, although numerous studies have shown aberrant activation in cortical areas in response to various tasks in schizophrenia,[37,75,76] our results suggest that such deficits could reflect underlying deficits in structures connected with the cortex such as the thalamus.[77,78] The extent to which the abnormal coupling between the thalamus and mSFG and the thalamus and insula can be attributed to dysfunction in thalamic activity per se, compared with the integrity of structural connections between these regions, requires further investigation.[79]

CLINICAL SIGNIFICANCE

Numerically, there was no overlap in the amplitude of TMS-evoked thalamic response between patients with schizophrenia and healthy subjects. Additionally, the thalamic response amplitude in patients showed a trend toward predicting the severity of positive symptoms, a result in accord with similar relationships observed with sleep spindle data.[26] Consequently, our results not only confirm the thalamic abnormality in schizophrenia but also show that it may be related to clinical symptoms.

FUTURE CHALLENGES

Several limitations of this investigation represent challenges for future research. First, although sleep spindle data suggest that thalamic deficits do not reflect a group difference in medication,[26] it will be necessary to replicate our results while controlling for effects of medication. Additionally, further investigation with first-degree relatives will be necessary for understanding the

potential genetic components of the abnormality in the thalamus. Investigating patients with first-episode schizophrenia will help discern whether the thalamic abnormality is present in early as well as later stages of the illness. Future studies will be required to assess the influence of potentially important demographic and diagnostic variables (eg, socioeconomic status, subtype).

A DEFICIT IN THE TRN?

The sleep spindle deficit in schizophrenia implicates a thalamic, and more specifically a TRN, abnormality in schizophrenia.[26] Because the TRN, a structure that surrounds the dorsal and lateral portions of the thalamus, is very thin (approximately 1 mm in cross section[80]), it is not possible to resolve it with conventional fMRI techniques. There are 2 reasons, however, to believe that the activity we measured in the thalamus is heavily weighted by contributions of the TRN. First, the sole efferents from the TRN are inhibitory projections to the underlying thalamus. (Thus, the totality of the synaptic activity attributable to TRN output will be reflected in the blood oxygen level–dependent signal from the principal thalamic nuclei that receive these outputs.) Second, synaptic activity in the TRN is likely to be larger in magnitude than synaptic activity in principal thalamic nuclei. This is because there are 3.7 times more excitatory glutamatergic corticothalamic synapses onto the TRN than onto principal thalamic nuclei and because excitatory postsynaptic currents are 2.5 times larger in the TRN than in thalamocortical neurons.[81] Consequently, it is plausible that the blood oxygen level–dependent signal we measured in the thalamus was heavily weighted by cortico-TRN-thalamic propagation of the spTMS-evoked response and that the decreased spTMS-evoked thalamic response in subjects with schizophrenia may reflect a more specific abnormality in the TRN.

Animal studies support the idea that the TRN is necessary for sensory gating and attention modulation,[82,83] brain functions aberrant in schizophrenia.[19,84,85] More evidence gleaned from animal models and higher-resolution imaging or postmortem studies in humans will be necessary to more fully test this hypothesis.

In summary, this study implicates an abnormality in the thalamus in the neurobiology of schizophrenia. This physiological abnormality cannot be attributed to differences in attention, compliance, or task performance that may exist between groups. Future studies will need to determine whether this deficit stems specifically from dysfunction of the TRN. More generally, this study underscores the value of concurrent spTMS-fMRI for probing the integrity of distributed neural circuits in psychiatric populations.

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Correction

Errors in Text. In the Original Article titled "Suicide Risk in Primary Care Patients With Major Physical Diseases: A Case-Control Study" by Webb et al, published in the March issue of the *Archives* (2012;69[3]:256-264), errors occurred in 2 places in the text. On page 256, the "Setting" portion of the Abstract should have read as follows: "Family practices in England (n=224) registered with the General Practice Research Database from January 1, 2001, through December 31, 2008. The case-control data were drawn from approximately 4.7 million complete patient records, with complete linkage to national mortality records." On page 257, in the first paragraph of the "Data Sets and Outcome Ascertainment" subsection of the "Methods" section, the fifth sentence should have read as follows: "The September 2010 version we analyzed contained approximately 4.7 million complete patient records from 224 family practices in England." Despite inaccuracies in the initial methodological description, the findings and implications of this study are unaltered.