

# Sensory Gating Endophenotype Based on Its Neural Oscillatory Pattern and Heritability Estimate

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**Context:** The auditory sensory gating deficit has been considered a leading endophenotype in schizophrenia. However, the commonly used index of sensory gating, P50, has low heritability in families of people with schizophrenia, raising questions about its utility in genetic studies. We hypothesized that the sensory gating deficit may occur in a specific neuronal oscillatory frequency that reflects the underlying biological process of sensory gating. Frequency-specific sensory gating may be less complex than the P50 response, and therefore closer to the direct genetic effects, and thus a more valid endophenotype.

**Objectives:** To compare the gating of frequency-specific oscillatory responses with the gating of P50 and to compare their heritabilities.

**Design:** We explored single trial-based oscillatory gating responses in people with schizophrenia, their relatives, and control participants from the community.

**Setting:** Outpatient clinics.

**Participants:** Persons with schizophrenia (n = 102), their

first-degree relatives (n = 74), and control participants from the community (n = 70).

**Main Outcome Measures:** Gating of frequency-specific oscillatory responses, gating of the P50 wave, and their heritability estimates.

**Results:** Gating of the  $\theta$ - $\alpha$ -band responses of the control participants were significantly different from those with schizophrenia ( $P < .001$ ) and their first-degree relatives ( $P = .04$  to  $.009$ ). The heritability of  $\theta$ - $\alpha$ -band gating was estimated to be between 0.49 and 0.83 and was at least 4-fold higher than the P50 heritability estimate.

**Conclusions:** Gating of the  $\theta$ - $\alpha$ -frequency oscillatory signal in the paired-click paradigm is more strongly associated with schizophrenia and has significantly higher heritability compared with the traditional P50 gating. This measure may be better suited for genetic studies of the gating deficit in schizophrenia.

*Arch Gen Psychiatry.* 2008;65(9):1008-1016

**A**BNORMAL SENSORY GATING may index the inability of people with schizophrenia to sufficiently filter unwanted sensory information and is considered a leading endophenotype in schizophrenia.<sup>1,2</sup> Sensory gating is efficiently probed using a simple paired-click auditory evoked potential paradigm; the gating response is reflected by a diminution of evoked potential response elicited by the second of a pair of identical auditory stimuli. Most previous sensory gating studies have focused on the averaged P50 wave in response to the auditory stimuli.<sup>3,4</sup> Such P50 gating impairments have been observed in people with schizophrenia and their relatives in many,<sup>5-8</sup> but not all<sup>9-11</sup> studies. More comprehensive review can be found elsewhere.<sup>4</sup>

Although it is often considered an endophenotype for schizophrenia, the traditional P50 gating measure has low heritability, which has been estimated at 0.10 in the families of people with schizophrenia.<sup>12</sup> Low heritabilities compromise the utility of this phenotype for genetic studies and even call into question the validity of the phenotype, given the high heritability of the schizophrenia phenotype.<sup>13</sup>

We sought to refine the sensory gating paradigm by studying single-trial oscillatory responses to an auditory stimulus, independent of any averaged waveforms. Schizophrenia is a disease associated with aberrant processing of sensory information. Sufficient data have shown that neuronal assemblies have the intrinsic capacity to oscillate at different frequencies in response to sensory input,<sup>14</sup>

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representing different stages of sensory information processing.<sup>14-16</sup> These oscillations constitute rhythmic modulations in neuronal excitability that affect the likelihood of spike output in response to subsequent input.<sup>17,18</sup> It is possible that a deficit in sensory gating can be more directly evaluated by examining the rhythmic modulatory process of sensory input rather than an averaged waveform, which may diminish the ability to examine the underlying oscillatory mechanism. We hypothesized that the sensory gating deficit in schizophrenia would be indexed by neural oscillations in a specific time frequency measurable on single trials. This may represent a more elementary physiological process and thus be more sensitive to the direct genetic effect underlying sensory gating, yielding higher heritability estimates compared with the averaged P50 wave. Using a discrete wavelet transform technique to identify single-trial oscillatory components contributing to sensory gating, we previously found that auditory responses are represented by a range of time frequency-specific oscillatory components, and that  $\beta$ - and, to a lesser extent,  $\alpha$ -frequency oscillations indexed the strength of P50 suppression in healthy controls.<sup>19</sup> In this study, we sought to identify single-trial scalp electrical oscillatory signals that are suppressed by repeated stimuli. Once such a signal was found, we tested whether it is a better endophenotype compared with P50, based on the following a priori endophenotype testing criteria: (1) its association with the schizophrenia phenotype; (2) its presence in family members without schizophrenia who are not taking antipsychotic medications; (3) whether it has significant heritability; and (4) if it is superior to the P50 gating measure, ie, provides better differentiation between control participants and persons with schizophrenia, between controls and family members of persons with schizophrenia, and higher heritability when compared with P50 gating.

## METHODS

### PARTICIPANTS

All participants were between the ages of 16 and 58 years, with no neurological conditions or current substance abuse or dependence. Patients with schizophrenia were diagnosed using the Structured Clinical Interview for *DSM-IV*.<sup>20</sup> Patients were recruited through our outpatient research programs and Baltimore-area mental health clinics. Four were taking a first-generation antipsychotic, 4 were not taking an antipsychotic, and the rest were taking second-generation antipsychotic agents. In addition, 18.6% were also taking a selective serotonin reuptake inhibitor and 9.8% were taking benzodiazepine. Patients taking benzodiazepine were asked to take the medication after testing on the day of testing. Clinical symptoms were assessed using the Brief Psychiatric Rating Scale. Global functions were measured by the Strauss-Carpenter Level of Function scale, with a higher score reflecting better functioning.<sup>21</sup> All available first-degree relatives of the subjects with schizophrenia were recruited. Controls were recruited using an epidemiological sampling method that aimed to recover the average status of the population instead of a "super-clean" cohort. The control subjects were randomly selected from a list of subjects who matched schizophrenia probands on age (within 3

years above or below the age of the probands), sex, ethnicity, and neighborhood (same zip code); the list was generated using the State of Maryland Motor Vehicle Administration registration. Control participants had no family history of psychosis for 3 generations. Available first-degree relatives of the controls were also recruited. Controls and relatives of patients with schizophrenia who did not have schizophrenia were screened using the Structured Clinical Interview for *DSM-IV* and identical inclusion/exclusion criteria. They had no *DSM-IV* psychotic or bipolar disorders. Controls and relatives with other Axis I disorders were accepted so that the group differences reflected differences in family history of schizophrenia alone and not in other psychiatric conditions. None of the subjects had participated in our previous study.<sup>19</sup> All subjects gave written informed consent in accordance with the University of Maryland institutional review board guidelines.

### SAMPLE SIZE FOR GROUP COMPARISONS

The analysis included 246 subjects: 102 with schizophrenia (93 probands and 9 of their relatives with schizophrenia), 74 first-degree relatives without schizophrenia, and 70 control participants from the community. Not included in the sample were 9 subjects who completed event-related potential recording but had excessive artifacts or had equipment problems during recording.

### SAMPLE SIZE FOR HERITABILITY ESTIMATES

This sample included 48 family units of subjects with schizophrenia, consisting of 48 probands and 75 first-degree relatives (with or without schizophrenia). The 48 families included 30 of size 2 (2 subjects per family), 11 of size 3, 6 of size 4, and 1 of size 6. In total, this set included 134 sibling-sibling or parent-offspring pairs used for the heritability estimate. The community control samples included 20 small families (20 probands and 23 first-degree relatives) but formed only 23 informative relative pairs.

## LABORATORY PROCEDURE

### Evoked Potential for P50

Evoked potentials were recorded and processed using the same procedures previously reported.<sup>22</sup> Smokers refrained from smoking for 1 hour prior to recording. Subjects sat in a semireclining chair in a sound chamber with their eyes open and listened to 150 paired-click stimuli (1-millisecond duration; 72 dB; 500-millisecond interclick interval; 10-second inter-trial interval). The electroencephalogram reading was sampled at 1 kHz (200-Hz low pass; 0.1-Hz high pass; 60-Hz notch filter applied during recording) to yield 500-millisecond epochs, including a 100-millisecond prestimulus window. Artifacts were removed from single trials, with a rejection criterion above or below 75 V, followed by visual inspection. The central channel was used because it provides the most prominent P50 gating.<sup>23,24</sup> The single-trial records were baseline corrected, 3 to 100 Hz (24 octave slopes) bandpass filtered, and averaged to obtain the P50 waves. The P50 response to the first stimulus (S1) was defined as the largest positive-going wave occurring 35 to 75 milliseconds after the stimulus, measured from the trough of the preceding wave to the P50 peak. The second stimulus (S2) P50 was set to  $\pm 10$  milliseconds of the latency to S1 P50.<sup>23</sup> The S2:S1 P50 ratio was P50 gating. The P50 was scored by the consensus of 2 raters without diagnostic or demographic information.

## Wavelet Extraction of Neural Oscillations

The same artifact-free single trials for P50 measurement were used here. Unlike Fourier transform, wavelet transform allows the detection of local variation in oscillations because it relies on wavelets of limited duration instead of unbound sine waves. Wavelet transform of single-trial recording has the advantage of not being biased by trial-to-trial temporal variability because it extracts both stationary and nonstationary energy, which should solve the P50 wave problem of different temporal variability between patients with schizophrenia and controls.<sup>25,26</sup> In the discrete wavelet transform (DWT) procedure, each decomposition level, termed *detail*, is orthogonal to the other details.<sup>27</sup> Because each detail has a unique frequency band, we can use DWT to separate electroencephalogram oscillatory signals into different frequency bands that are mathematically independent of the others. This property of the DWT is advantageous over the more commonly used continuous wavelet transform in this context, because the latter yields continuous frequency bands, the separation of different frequency bands is somewhat arbitrary, and the neighboring bands are not necessarily independent of each other. The theory and methodology of using DWT to decompose evoked energy have been examined by simulation and tested in a large cohort of controls.<sup>19</sup> We used an 8-level discrete biorthogonal wavelet,<sup>27,28</sup> referred to as *bio5.5* (Wavelet Toolbox; MathWorks Inc, Natick, Massachusetts), to separate evoked energy into 8 details (D1 to D8) that represent 8 frequency bands. An example of the single-trial DWT decomposition is presented in **Figure 1**. By simulation, we estimated the frequency band of each detail: D3 corresponded to very fast  $\gamma$ -frequency activities greater than 85 Hz (D4, 40-85 Hz; D5, 20-40 Hz; D6, 12-20 Hz; D7, 5-12 Hz). Bands D1, D2, and D8 were not included because D1 and D2 represented very high frequency noise and the frequency at D8 was too low to be resolved given the small time window between S1 and S2. The rationale to use this wavelet is described in more detail elsewhere.<sup>19</sup>

To evaluate the temporal development of the oscillatory response after the wavelet transform, each 500-millisecond detail was divided into four 125-millisecond epochs (T0, -100-25 milliseconds; T1, 26-150 milliseconds; T2, 151-275 milliseconds; T3, 276-400 milliseconds) (**Figure 2**). Energy within each epoch of each frequency band (detail) was measured by power spectrum density (PSD) using the nonparametric Welch method.<sup>29,30</sup> A time-frequency component was the PSD of each epoch of a detail. This process was repeated for S2. Sensory gating of each time-frequency component was calculated as the S2:S1 PSD ratio and was averaged across all trials for each participant. This method of measuring sensory gating is based entirely on computerized algorithms.

## STATISTICAL ANALYSIS

The dependent measures (S1 PSD, S2 PSD, S2:S1 PSD ratio) were compared between groups using a mixed model for unbalanced repeated measures analysis of variance, which takes into account the correlations in phenotype between subjects from the same family (PROC MIXED in SAS; SAS Inc, Cary, North Carolina) by including family as a random effect. Frequency band (D3 through D7) and epoch (T0 through T3) were within-subject factors, and diagnosis (patients, unaffected relatives, controls) was the between-group factor. Significant effects were followed up by repeated measures analyses of variance testing of the diagnosis  $\times$  epoch interaction for each frequency band, applying a Bonferroni correction for comparisons of 5 frequencies ( $P < .01$ ). Post hoc tests of the significant models for effects of diagnosis and epoch were consid-

ered secondary analyses and reported without  $P$  value adjustment for multiple comparisons.

The heritability of each measure, which reflects the proportion of the variance attributed to additive genetic effects, was calculated using variance components analysis implemented in the SOLAR (Sequential Oligogenic Linkage Analysis Routines; Southwest Foundation for Biomedical Research, San Antonio, Texas) software program.<sup>31</sup> The total variance of a phenotype was partitioned into a genetic component owing to additive polygenic effects and a random environmental component. We initially assessed the effects of age and sex on each phenotype and, when significant, adjusted for the effects of these variables in the heritability analyses. Statistical significance of heritability was determined by comparing log likelihoods between the polygenic model and the sporadic model, where the heritability was constrained at 0.<sup>12,32</sup> We also tested whether the heritability of gating of an oscillatory component differed significantly from the heritability of P50 gating; this was tested by calculating the heritability of the sensory gating of an oscillatory component phenotype, after constraining the likelihoods on the heritability of the P50 gating phenotype.

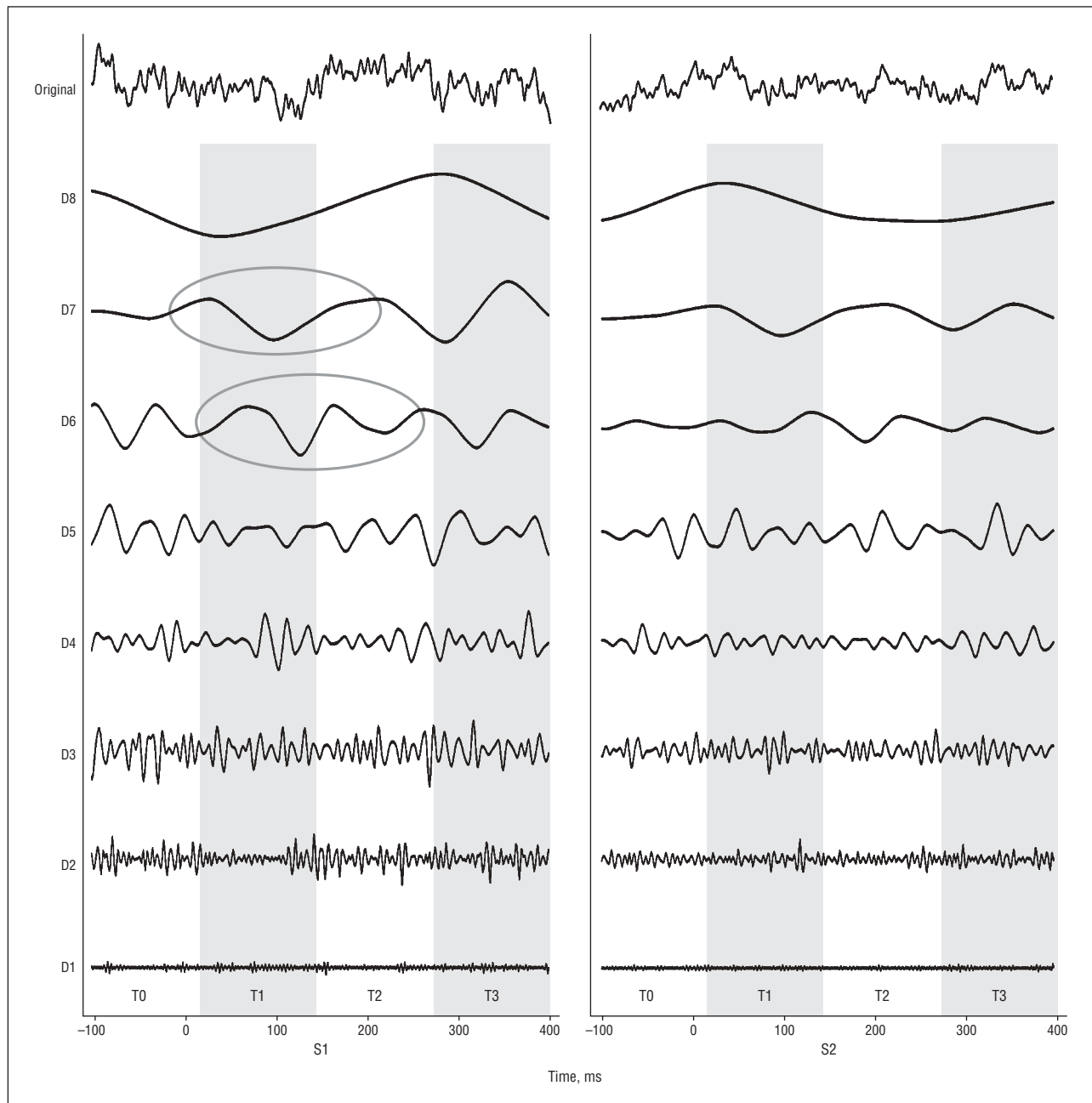
## RESULTS

### DEMOGRAPHIC AND P50 GATING

Controls, patients with schizophrenia, and relatives without schizophrenia were not significantly different in age (mean [SE], 40.4 [1.5], 39.1 [1.2], and 43.6 [1.4] years, respectively;  $P = .10$ ) but did significantly differ in the ratio of men to women (39:31, 74:28, and 24:50, respectively;  $\chi^2 = 28.0$ ;  $P < .001$ ), mainly owing to a disproportionate number of female relatives. Smoking status (whether or not the person smoked cigarettes habitually) differed among controls (21.4%), patients with schizophrenia (54.9%), and relatives without schizophrenia (12.5%) ( $\chi^2 = 39.68$ ;  $P < .001$ ). Relatives without schizophrenia did not significantly differ from controls on any Axis I psychiatric diagnosis or smoking status (all  $\chi^2 < 3.37$ ; all  $P > .18$ ). Mean (SE) percentages of rejected trials for controls, patients, and relatives were 21.8% (0.02%), 25.8% (0.02%), and 21.3% (0.02%), respectively ( $F_{2,244} = 2.78$ ;  $P = .06$ ) and had no significant correlation with any gating measures (data not shown). The mean (SE) P50 ratios did not differ significantly between groups either before (controls, 0.56 [0.04]; patients, 0.62 [0.03]; relatives, 0.60 [0.04];  $F_{2,244} = 0.55$ ;  $P = .58$ ) or after ( $P = .32$ ) accounting for differences in sex. Mean (SE) of the P50 ratio of patients who smoke (0.61 [0.05]) did not significantly differ from patients who do not smoke (0.62 [0.05];  $F_{1,101} = 0.06$ ;  $P = .80$ ). There were also no significant group differences between controls, patients, and relatives in mean (SE) S1 (4.04 [0.37]  $\mu$ V, 3.91 [0.35]  $\mu$ V, and 3.31 [0.32]  $\mu$ V, respectively;  $F_{2,244} = 1.11$ ;  $P = .33$ ) or S2 amplitudes (2.01 [0.20]  $\mu$ V, 2.32 [0.28]  $\mu$ V, and 2.01 [0.28]  $\mu$ V, respectively;  $F_{2,244} = 0.47$ ;  $P = .62$ ).

### DETERMINATION OF WHICH OSCILLATORY COMPONENT IS GATED DURING SENSORY GATING AND WHICH MARKS SCHIZOPHRENIA LIABILITY

Mixed-effect analyses of variance on the S2:S1 PSD ratios showed that there was a diagnosis  $\times$  detail



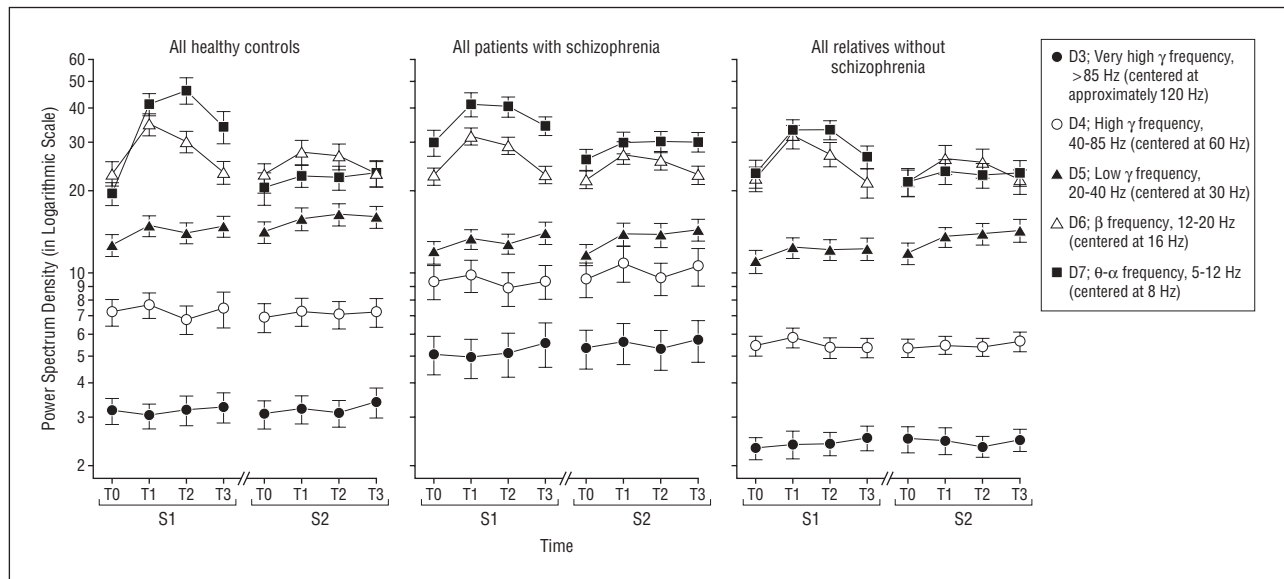
**Figure 1.** An illustration of 8-level bio5.5 discrete wavelet decomposition on a single-trial recording in response to the first (S1) and second (S2) stimuli. Time 0 indicates the onset of stimuli. Each 500-millisecond epoch was divided into four 125-millisecond epochs (T0-T3) for the purpose of extracting the temporal evolution of the power spectrum density. All details (D1-D8, representing frequency bands) are plotted on the same y-axis, ranging from -12 to +12 on the wavelet scale. There were no discernible signals that could be easily observed from the original single-trial recording (top). With the wavelet transform, it appeared that discernible energy changes might have appeared at the areas marked by ovals, which appeared attenuated in response to S2.

interaction ( $F_{8,4707}=6.24$ ;  $P<.001$ ), a detail  $\times$  epoch interaction ( $F_{12,4707}=15.09$ ;  $P<.001$ ), and a main effect of detail ( $F_{4,4707}=146.89$ ;  $P<.001$ ). Gating ( $S2:S1 < 1$ ) occurred primarily at D6 ( $\beta$  frequency) and D7 ( $\theta$ - $\alpha$  frequency), while most of D3 through D5 ( $\gamma$  frequencies) did not show gating, but rather a tendency toward facilitated responses during S2 ( $S2:S1 > 1$ ) (**Figure 3**).

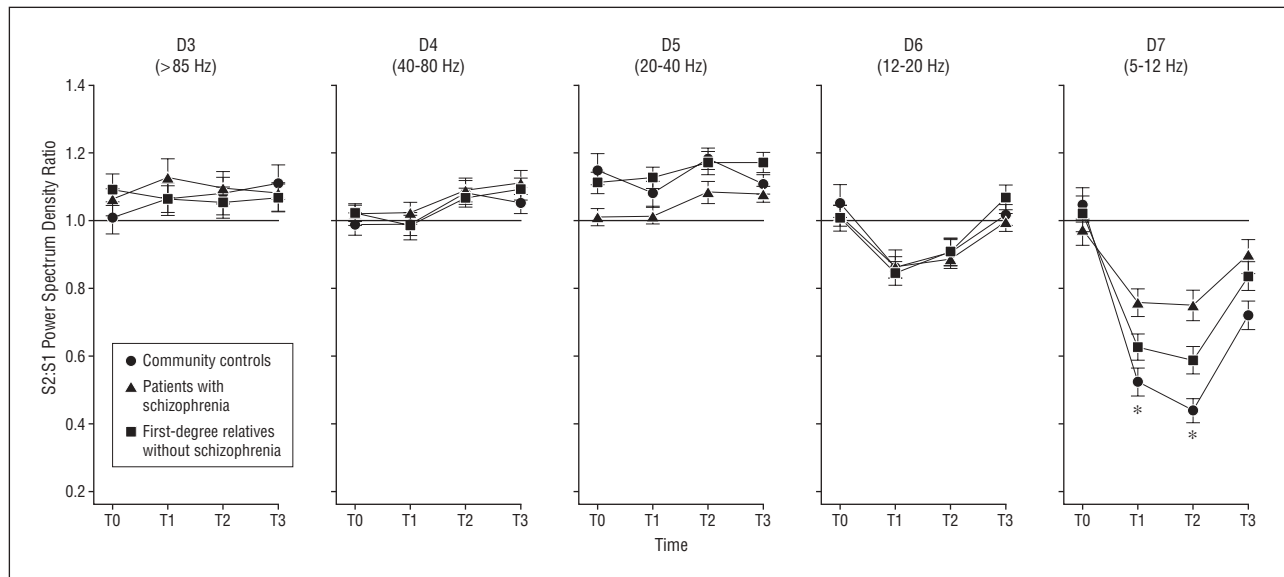
For  $\gamma$  frequencies, there was no statistically significant diagnosis effect or epoch  $\times$  diagnosis interaction for D3 or D4 (Figure 3). At D5, there were significant effects of diagnosis ( $F_{2,243}=5.75$ ;  $P=.004$ ). Post hoc tests

showed that controls ( $P=.03$ ) and relatives ( $P=.001$ ) have elevated D5 ratios compared with patients. However, this measure did not significantly differentiate controls from relatives ( $P=.41$ ).

At  $\beta$  frequency (D6), there was a significant effect of epoch ( $F_{3,576}=31.41$ ;  $P<.001$ ). Epochs T1 ( $t_{245}=8.43$ ;  $P<.001$ ) and T2 ( $t=5.33$ ;  $P<.001$ ), but not T3 ( $P=.99$ ), had significantly more gated responses compared with the baseline (T0), indicating that gating occurred at the  $\beta$  frequency in the 26- to 275-millisecond window (Figure 3). However, there was no significant effect of diagnosis ( $P=.80$ ) or diagnosis  $\times$  epoch interaction



**Figure 2.** Oscillatory patterns in response to first (S1) and second (S2) stimuli in control participants from the community ( $n=70$ ), patients with schizophrenia ( $n=102$ ), and their relatives ( $n=74$ ). Error bars are standard errors. Time points T1 through T3 indicate 125-millisecond epochs.



**Figure 3.** Gating of  $\beta$  and  $\theta$ - $\alpha$  oscillatory components. A ratio of 1 indicates no gating; less than 1 indicates a gated response to the second stimulus (S2); more than 1 indicates facilitated response to S2. Error bars are standard errors. D1 through D8 indicate details representing frequency bands; S1, first stimulus; T0 through T3, 125-millisecond epochs. \* Both subjects with schizophrenia ( $n=102$ ) and their first-degree relatives ( $n=74$ ) showed significantly reduced sensory gating in this time-frequency component compared with controls ( $n=70$ ).

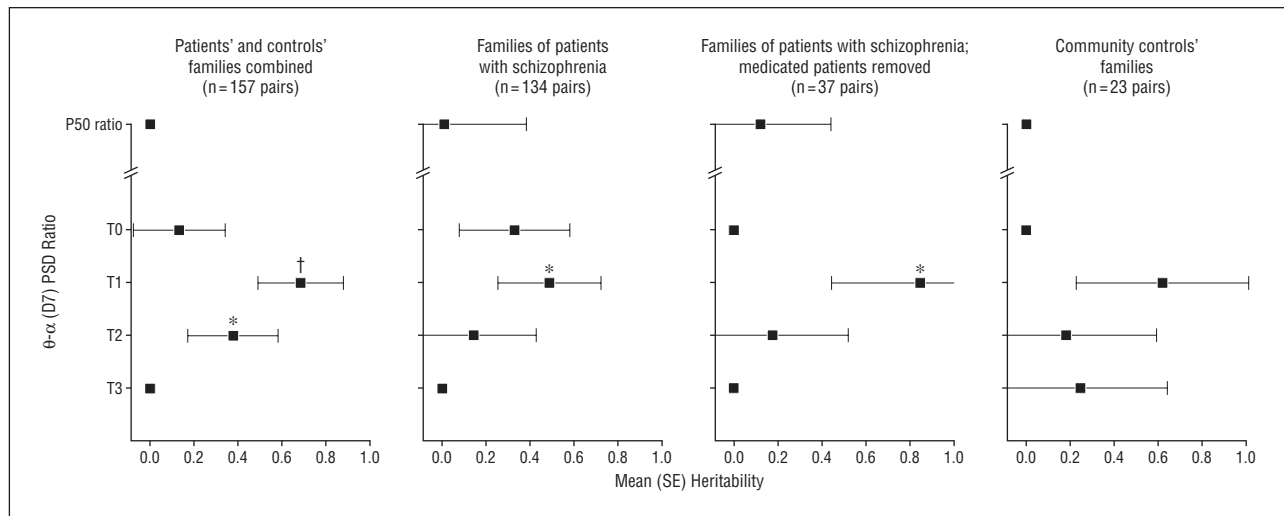
( $P = .52$ ), suggesting that  $\beta$ -band gating is not a schizophrenia endophenotype.

At  $\theta$ - $\alpha$  frequency (D7), there were significant effects of epoch ( $F_{3,480} = 85.48$ ;  $P < .001$ ), diagnosis ( $F_{2,243} = 8.43$ ;  $P < .001$ ), and their interaction ( $P < .001$ ). There was no group difference at T0 ( $P = .68$ ). There was a significant group difference at T1 ( $F_{2,245} = 10.56$ ;  $P < .001$ ). Patients ( $P < .001$ ; effect size in Cohen  $d = 0.68$ ) and their relatives ( $P = .04$ ; effect size in Cohen  $d = 0.38$ ) had significantly reduced gating compared with controls. There was also a significant group difference at T2 ( $F_{2,245} = 15.78$ ;  $P < .001$ ). Patients ( $P < .001$ ; effect size in Cohen  $d = 0.84$ ) and their relatives ( $P = .009$ ;  $d = 0.51$ ) had significantly reduced gating compared with controls. Finally, there was

a significant group difference at T3 ( $F_{2,245} = 4.84$ ;  $P = .009$ ). Patients ( $P = .002$ ), but not their relatives ( $P = .05$ ), had significantly reduced gating compared with controls. Sex or smoking status was not a significant covariate in any of the analyses (all  $P \geq .23$ ). This suggested that gating of the  $\theta$ - $\alpha$  band in the 25- to 275-millisecond window fulfilled the first 2 criteria for a schizophrenia endophenotype.

#### DETERMINING WHETHER $\theta$ - $\alpha$ -BAND GATING IS HERITABLE

In the combined sample of both controls' and patients' families, gating of the  $\theta$ - $\alpha$  oscillations was significantly



**Figure 4.** Heritability ( $h^2$ ) estimates of different sensory gating components. Error bars are standard errors. If  $h^2=0$ , no standard errors are calculated. Note that the most heritable component resides at the T1 (26-150 milliseconds) epoch (T1 through T3 represent 125-millisecond epochs) across different groupings. D7 indicates detail 7, representing the  $\theta$ - $\alpha$ -frequency band; PSD, power spectrum density. \*  $P < .05$ . †  $P < .01$ .

heritable ( $h^2$ ) at T1 (mean [SE]  $h^2=0.68$  [0.19];  $P < .001$ ;  $n=157$  pairs) and T2 (mean [SE]  $h^2=0.38$  [0.20];  $P=.03$ ) (Figure 4). In patients' families alone, the mean (SE) heritability was also significant at T1 ( $h^2=0.49$  [0.24];  $P=.02$ ;  $n=134$  pairs). The standard errors of the estimates were wide owing to the modest sample size. Medication effects, such as effect of clozapine on sensory gating,<sup>33,34</sup> if present, might bias the true heritability because they would affect only the subjects with schizophrenia. Excluding patients taking clozapine ( $n=18$ ), the mean (SE) heritability at T1 was 0.50 (0.23) ( $P=.02$ ). Excluding patients taking any antipsychotic agents, the mean (SE) heritability at T1 actually increased ( $h^2=0.84$  [0.40];  $P=.03$ ), although this estimate was based on only 37 related pairs from 18 families. The mean (SE) heritability estimate at T1 in the community controls' families was similar to that in the patients' families ( $h^2=0.62$  [0.39];  $P=.09$ ;  $n=23$  pairs), although the estimate did not differ significantly from 0, possibly owing to the small sample size.

In comparison, the heritability of the P50 ratio ranged from 0.00 to 0.12 in the different diagnostic groups (Figure 4), with none achieving statistical significance. All of the significant  $\theta$ - $\alpha$  PSD-gating heritability estimates differed significantly from the point estimates obtained when constrained to those for the P50 gating phenotype ( $h^2=0-0.12$ ), suggesting that the genetic loading of D7 gating was significantly higher than that of the P50 gating.

#### COMPARISON OF INDIVIDUAL RESPONSE TO STIMULUS WITH RESPONSE GATING IN MARKING SCHIZOPHRENIA LIABILITY

Previous studies showed that an abnormal ratio may not necessarily reflect a gating problem because response to S1 alone could account for the impaired (P50) ratio in persons with schizophrenia.<sup>25,26,35</sup> To examine whether this applies to the oscillatory measures, we analyzed the  $\theta$ - $\alpha$ -band responses to individual stimuli (S1 and S2). For response to S1, there were no significant group dif-

ferences in T1, T2, or T3 epochs ( $P \geq .07$ ). For response to S2, there was a significant group difference at T2 ( $P=.04$ ), but not at T1 or T3 (both  $P=.07$ ). Post hoc analysis showed that subjects with schizophrenia had elevated S2 PSD compared with controls ( $P=.04$ ) at T2, suggesting that the gating dysfunction in persons with schizophrenia was in part produced by an insufficient inhibition of the response to S2. However, controls and relatives were not significantly different in this time-frequency component ( $P=.93$ ), ruling out the possibility that S2 response alone was better than the PSD ratio for marking schizophrenia liability.

Finally, we explored individual responses in other frequency bands. In none of the other time-frequency components were there measures that significantly and simultaneously differentiated patients and relatives from controls. A notable observation was that patients showed elevated  $\gamma$ -frequency activities compared with controls and relatives ( $P=.03$  and  $.003$  for D3 and D4 in response to S1 and S2; Figure 2). Relatives and controls showed no significant differences. An exploration of potential medication effects failed to find conclusive evidence linking specific psychotropic medications to the elevated  $\gamma$ -frequency responses in patients (data not shown).

Heritabilities of the individual  $\theta$ - $\alpha$ -band response to S1 and S2 were not significant in any epoch (all  $h^2 \leq 0.30$ ; all  $P \geq .10$ ). Heritabilities of the response in other time-frequency components (all  $h^2 \leq 0.40$ ) were lower than that of  $\theta$ - $\alpha$ -band gating. In summary, none of the responses in the  $\gamma$ - to  $\beta$ -frequency range can simultaneously separate both patients and unaffected relatives from controls; none of their heritability estimates were higher than those of the  $\theta$ - $\alpha$  gating.

#### CLINICAL CORRELATES

Gating of D7 (mean of T1 and T2) was significantly correlated with Brief Psychiatric Rating Scale total score ( $\rho=0.22$ , Spearman rank correlation;  $P=.03$ ), psychosis

( $\rho=0.31$ ;  $P=.003$ ), thought disorder ( $\rho=0.28$ ;  $P=.007$ ), and hostility ( $\rho=0.29$ ;  $P=.007$ ) subscales, but not withdrawal, anxiety, or activation subscales (all  $\rho < 0.15$ ; all  $P > .13$ ), suggesting that poor gating was weakly but significantly associated with more psychotic symptoms in subjects with schizophrenia. The D7 gating was also significantly correlated with the level of function score ( $\rho=-0.30$ ;  $P < .001$ ), suggesting that poor gating was correlated with poor overall function. In comparison, P50 gating was not significantly correlated with any Brief Psychiatric Rating Scale scores (all  $P \geq .19$ ) or level of function ( $P=.90$ ) scores.

## COMMENT

This study applies modern signal processing methods to explore oscillatory signals that are suppressed during repeated stimuli. The results indicate that gating of auditory evoked oscillatory responses occurs primarily at the  $\theta$  to  $\beta$  frequencies when measured in single trials. Gating of the  $\theta$ - $\alpha$  band marks the liability for schizophrenia and is heritable; its heritability is estimated to be at least 4-fold higher than that of the traditional P50 gating measure in the families of people with schizophrenia.

The heritability of the P50 gating measure was estimated to be from 0.00 to 0.12. Several twin studies of P50 gating in populations without schizophrenia suggested that its heritability could be estimated to be as high as 0.40 to 0.68 by some genetic models.<sup>36-39</sup> However, these twin-based estimates may be misleading for family studies because they used models that relied heavily on the familial correlations of the monozygotic twins. For instance, the familial correlations of P50 gating in dizygotic twins (50% genetic sharing) were 0.00<sup>36</sup> and 0.04,<sup>38</sup> though the heritability estimates were reported to be 0.44 and 0.68, respectively, in these studies. Genetic sharing in first-degree family members is 50%. Therefore, data from these twin studies could have actually predicted that the P50 gating measure is unlikely to have a high heritability in family samples, which is confirmed by the recent Consortium of the Genetics of Schizophrenia sample ( $h^2=0.10$ )<sup>12</sup> and now by our sample.

Sensory gating has been considered one of the leading endophenotypes of schizophrenia. However, the use of P50 gating as the primary index for sensory gating has been questioned owing to its low test-retest reliability<sup>9,40,41</sup> and is further discouraged recently by its low heritability in families of people with schizophrenia. Several alternative measures to P50 have been examined.<sup>25,26,42-49</sup> For example, using frequency-domain analyses, it was found that gating of the lower-frequency response (approximately 1-20 Hz) of the averaged evoked potential provided better separation between patients and controls than P50 or  $\gamma$ -band gating.<sup>42-44</sup> Another approach was to use evoked potentials occurring in the 100- to 200-millisecond post-stimulus interval, namely, the N1 and P2 components, which illustrated significant differences between patients and controls in some studies<sup>41,43-45</sup> but produced the opposite finding in a study of first-degree relatives.<sup>50</sup>

These prior efforts suggest that sensory gating can occur at a lower frequency and in a window after the P50 wave, though a systematic evaluation of these alternative measures' heritability in the families of people with schizophrenia has not been reported. Our finding of impaired single-trial  $\theta$ - $\alpha$ -band gating at the 25- to 275-millisecond window may be viewed as consistent with these prior data. However, we have only compared the current wavelet approach with P50. It would be informative to compare it with other alternative processing approaches in the future.

While we have used sensory gating to describe both P50 and  $\theta$ - $\alpha$ -band gating, there is a lack of direct evidence to support or refute whether P50 gating and  $\theta$ - $\alpha$ -band gating are measuring the same underlying information processing. There was a lack of substantial correlation between the 2 gating measures (Pearson  $r=0.01-0.13$  in different epochs). On the other hand, P50 is a time-locked response, while the  $\theta$ - $\alpha$  response includes time-locked and nonstationary responses; therefore there is probably some overlap in their underlying mechanism, but additional studies are clearly needed to understand the convergent and divergent mechanisms of the 2 gating phenomena. The new measure of gating is based on the decomposition of evoked energy into its oscillatory components in different frequency bands. This frequency-specific oscillatory gating measure is thought to be more elementary than the traditional P50 measure that is based on the averaged signal across all frequencies. The high heritability and impairment in unaffected relatives suggest that this new oscillatory gating measure indexes a biological process associated with the genetic liability for schizophrenia.

The finding that suppression at the  $\beta$  and  $\theta$ - $\alpha$  frequencies is the primary event during sensory gating is supported by a recent sensory gating study using a single-trial, independent component analysis-based approach, which showed that it was  $\theta$ ,  $\alpha$ , and  $\beta$  activities that contributed to N1 suppression.<sup>51</sup> So how might a failure in suppressing low-frequency oscillations be related to schizophrenia pathology and its liability? The data from this study demonstrated a genetic effect but did not address the physiological origin of the problem; therefore we should emphasize that the following discussion is speculative. Elevated ongoing low-frequency activity delays behavioral response in humans<sup>52</sup> and weakens the synchronization of interneuronal spiking in animal recordings.<sup>15</sup> The sensory gating problem has long been theorized as related to the inability of people with schizophrenia to filter out unwanted sensory information, leading to psychotic symptoms.<sup>1,2,53,54</sup> The identification of failed low-frequency gating in schizophrenia may suggest that a dysfunction in suppressing  $\theta$ - $\alpha$  activities in response to repeated stimulus might lead to impaired neuronal synchronization in response to subsequent sensory information. There was a modest but significant correlation between  $\theta$ - $\alpha$  gating and psychotic symptoms and/or level of function, suggesting that this deficit may be associated with clinical functions. However, additional human and animal studies are needed to test and expand this hypothesis. We should emphasize that it was the gating of the  $\theta$ - $\alpha$  response, not the actual responses,

that had higher heritability, suggesting that the  $\theta$ - $\alpha$  inhibition indexes a more elementary or distinct biological process separate from the process of individual responses (see limitation discussed below).

Low-frequency activities are related to reduced alertness. A question is whether the sedating effects of psychotropic medications contributed to the  $\theta$ - $\alpha$  gating abnormality. The finding of  $\theta$ - $\alpha$  gating deficits in unaffected relatives is inconsistent with a direct medication or chronic disease effect.

The traditional approach of using P50 to index sensory gating is also problematic owing to its measurement procedures; although the scoring is semiautomated, it still requires some subjective decisions to select the P50 peak within a window where there may be more than 1 peak or the selection of trough, which may be affected by the descending slope of the previous wave. This may add further noise to the data. In comparison, the DWT-based single-trial method, while computationally intense, does not require rater intervention, thus removing potential subjective biases. However, single-trial analysis also has its own inherent limitations because it includes the background noise. The sensory gating measure partially circumvents the problem because the ratio measure removes noise that is equally present in responses to S1 and S2. However, this limitation would be present when responses to individual stimuli are analyzed and may partially contribute to their lower ability to differentiate groups and their lower heritability estimates.

This study supports the hypothesis that the gating deficit represents an elementary neuronal dysfunction in persons with schizophrenia.<sup>55,56</sup> The deficit in gating of evoked responses remains a critical biomarker for the liability of schizophrenia and is highly heritable. However, frequency-based analytic methods are needed to facilitate the use of this endophenotype in genetic studies. This finding is especially timely and relevant given that a large amount of sensory gating data has already been collected in many laboratories. If our finding can be replicated by other laboratories, this or similar methods may be used to reanalyze existing data. The neural oscillatory approach may also provide a new framework for studying the neurobiological pathway of sensory gating and for testing novel compounds that can reverse specific oscillatory dysfunctions.

**Submitted for Publication:** January 28, 2008; final revision received May 3, 2008; accepted May 5, 2008.

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**Financial Disclosure:** None reported.

**Funding/Support:** This study was supported by grants MH49826, MH79172, MH77852, MH70644, MH68282, MH67014, and MH68580 from the National Institute of Mental Health, grant M01-RR16500 from the Neurophysiology Core of the University of Maryland General Clinical Research Center, and the Veterans Affairs Capitol Health Care Network (Veterans Integrated Services Network 5) Mental Illness Research, Education, and Clinical Center.

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