

Effects of Temporal Variability on P50 and the Gating Ratio in Schizophrenia

A Frequency Domain Adaptive Filter Single-Trial Analysis

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Background: Deficits in attention and cognition are common in schizophrenia. Using an auditory dual-click paradigm, a number of studies have found that, compared with normal controls, patients with schizophrenia show impaired inhibition, or gating, of repeated stimulation as measured by the average P50 evoked response to the second click. Since responses to many trials are collected to study the average response, fluctuations in the timing of the P50 response from trial to trial may influence the differences observed. We present a computerized, objective procedure that evaluates temporal variability in brain responses of patients with schizophrenia.

Methods: Ten normal controls and 10 patients diagnosed with schizophrenia were studied using the dual-click procedure. For each single trial, the temporal shift in P50 that yielded the best alignment with the average P50 response was used to derive a measure of P50 temporal

variability from trial to trial and to form P50 averages corrected for temporal variability.

Results: Patients with schizophrenia had significantly more temporal variability than normal controls. Correction for temporal variability in the P50 responses increased the size of P50 for both patients with schizophrenia and normal controls. Patients with schizophrenia had smaller P50 responses to the first click than controls and less inhibition to the second click before, but not after, correction for temporal variability.

Conclusions: These findings suggest that temporal variability contributes significantly to the P50 response as measured using the gating procedure. The measure of temporal variability may provide a new index of inhibitory and attentional function in schizophrenia.

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DEFICITS IN information processing and attention are common in individuals with schizophrenia.¹⁻⁴ Historically, the central hypothesis proposed to account for these deficits was that patients with schizophrenia fail to inhibit, or gate, sensory input, leading to sensory inundation and an overload of information reaching consciousness,⁵⁻⁷ possibly because of a defect in subcortical and cortical inhibitory pathways.⁸⁻¹¹ According to this hypothesis, problems of perception and attention in schizophrenia, such as hyperalertness and poor selective attention, are caused by the inability to filter (or gate) sensory input. The auditory dual-click paradigm has been used to compare sensory gating and inhibitory mechanisms in normal controls and patients with schizophrenia.⁸⁻¹⁹ In this procedure, paired clicks are presented, separated by an interval of approximately 500 milliseconds. The relative decrease

of the P50 wave of the average auditory evoked brain potential (EP) (**Figure 1**, top) to the second click (S2) compared with the first (S1) (S2/S1 ratio) has been used as a measure of effective sensory gating.⁸ The abnormal auditory gating observed in schizophrenia (reduced S2/S1 ratio)⁸⁻¹⁹ is reportedly a “fixed trait”⁹ that is genetically associated.^{20,21}

Decreased amplitude of the P50 wave to S1 in patients with schizophrenia compared with controls, reported by several of the investigators who originally observed impaired sensory gating,^{8-10,19,22,23} has been cited as a second P50 abnormality in schizophrenia.²³ Jin et al²⁴ found that increased variability in the timing of the trial-by-trial EPs of patients with schizophrenia accounted for decreased P50 amplitudes to S1 and contributed significantly to the gating effect. However, Freedman et al²⁵ have questioned whether single-trial analysis of the P50 response can extract a signal from noise. After selecting the largest peak in a window of 40 to

SUBJECTS AND METHODS

SUBJECTS

Ten normal controls (6 women, 4 men; mean±SD age, 26.5±3.5 years) and 10 individuals with schizophrenia (4 women, 6 men; mean±SD age, 33.1±7.6 years) who participated in the study of Jin et al²⁴ were the subjects in this study. Data from these subjects were included to determine whether the results of Jin et al²⁴ which were obtained using a semiautomated procedure to find P50 in the single trials, could be replicated using our objective, computerized procedure. The diagnosis of schizophrenia was made by 2 independent psychiatrists using *DSM-III-R* criteria and the Structured Clinical Interview for the *DSM-III-R* (SCID). Patients were free of medication for at least 5 days at the time of the study; prior to that, they had been receiving standard neuroleptics. The average age of onset of schizophrenia was 22.2 years (range, 13-29 years), and the average duration was 14.2 years (range, 1-30 years). Normal controls were interviewed by a psychiatrist and screened by questionnaire to confirm the absence of a personal or family history of mental illness.

PROCEDURE

P50 Collection

The P50 responses were acquired in the manner described by Jin et al.²⁴ A series of 100-dB sound pressure level¹⁴ paired clicks separated by 500 milliseconds were presented at 10-second interpair intervals through headphones. Evoked

potentials were collected using electrodes placed at Cz referenced to linked mastoids. Forty 180-millisecond epochs, bandpass filtered to include frequencies between 0.56 and 500 Hz, were sampled by a 16-bit A/D converter at the rate of 2756 points per second for each trial. An electro-oculogram was recorded so that trials contaminated by eye movements or blinking could be excluded from the averages and single-trial analysis.

Single-Trial Analysis

The single-trial analysis method used here was adapted from the procedure of Arpaia et al,⁴⁷ the correlational-template procedure of Woody³⁸ implemented in the frequency domain using the frequency characteristics of the waveform. In the time domain correlational-template procedure, the individual peak shape for a given component of the average waveform is used as an initial template. Each sweep is prefiltered to attenuate high-frequency activity unrelated to the signal and then shifted along the template to determine the temporal shift that gives the maximum correlation between the template and the single trial. This point of maximum correlation defines the latency of a given peak. The search window is set to minimize the possible misidentification of a preceding or succeeding peak of the same polarity and large enough to accommodate the expected peak.

The same procedure can be applied in the frequency domain using our adaptive filter technique, termed the *frequency domain adaptive filter* (FDAF).⁴⁷ The latency giving the maximum value of the cross-covariance function between the template and single trial (covariance is correlation times the product of the SDs of the variables) can be

80 milliseconds, they observed that the EPs selected from prestimulus and poststimulus periods did not differ in amplitude, suggesting to them that a reliable peak could not be selected using their single-trial procedure.

A number of early studies using cross-correlation techniques (which measure the association between successive time segments of EP waves) have provided support for the finding of Jin et al²⁴ by observing increased variability in the EPs of patients with schizophrenia,²⁶⁻³⁷ often in the EP region where P50 is located.^{26,28-30,33} More recent studies of EP variability in schizophrenia using the correlational template procedure³⁸ have reported reduced amplitudes and increased variability for the later components of the EP.^{37,39,40} In this procedure, correlations between a template (usually the average EP) and the single-trial EP are obtained.^{38,41-46} The point of maximum correlation is used to estimate the latency of the peak of the EP trial by trial, derive a measure of temporal variability among the single trials, and form a corrected average EP by aligning the single-trial EPs according to their estimated latency (Figure 1, bottom).

In this study, the correlational template method was implemented in the "frequency domain" (using the frequency instead of timing characteristics of the waveform) using a mathematical procedure called fast Fourier transform (FFT).⁴⁷⁻⁴⁹ This technique was used to measure P50 temporal variability and derive latency-

corrected averages, to test whether patients with schizophrenia have more temporal variability than controls, and to examine the effects of temporal variability on P50 amplitude and the gating ratio.⁵⁰

RESULTS

SINGLE-TRIAL ANALYSIS

For the normal control group, the amplitude of the P50 component to S1 and especially to S2 (preceding trough to peak) was enhanced by the FDAF procedure (Figure 3). The single-trial procedure produced an enhancement of the P50 for 9 of 10 control subjects for S1 and S2 (Figure 4, left). The amplitude enhancement (between the average and the fifth iteration) for normal controls ranged between 0.17 and 3.20 μ V for S1 (mean, 0.97 μ V) and between 0.59 and 3.53 μ V (mean, 1.37 μ V) for S2. For patients with schizophrenia, the single-trial procedure resulted in an enhancement of the P50 for 10 of 10 subjects for both S1 and S2 (Figure 3, right 2 panels). The amplitude enhancement ranged between 0.52 and 2.64 μ V (mean, 1.57 μ V) for S1 and between 0.12 and 5.61 μ V (mean, 1.99 μ V) for S2. For 2 normal controls, the bandpass for the FDAF procedure was raised to 40 to 62 Hz because of the absence of a distinct separation between P30 and P50 (subjects N1 and

derived using a mathematical algorithm involving the multiplication of the FFT of the 2-time series (ie, template and single trial).^{51,52} The complex conjugate (the imaginary part of a complex number multiplied by -1) product of the FFT of two time series is the FFT of their cross-covariance function.^{47-49,51,52} The latency corresponding to the maximum value of the cross-covariance function is found, and the trial is shifted by the latency that gives this maximum value. The shifted trials are then averaged to form a new template, and the new template is used to perform another iteration. The FDAF procedure uses the prefiltered data only to calculate the cross-covariance function; unfiltered data are used to generate the new template.⁴⁷

In the implementation of the FDAF procedure in this study, a series of steps were used for each subject. (1) A set of raw data for each click was generated. (2) Trials contaminated by major artifact (± 75 μ V) were automatically rejected. (3) The data were filtered to exclude high-frequency activity above 80 Hz to reduce the likelihood that the FDAF procedure would amplify noise. (4) For S1 and S2 separately, an average P50 was created that served as the initial template. (5) The search window parameters (window width, center point, maximum latency shift in P50 allowed within the window, and bandpass filter setting) were defined using the grand averaged P50 for all the subjects in this study, as well as the expected latency and frequency range of P50 cited in the literature^{8-11,13,53}: (a) the bandpass filter was defined between 25 and 62 Hz to include activity in the range of P50 (maximum attenuation was at 15 and 80 Hz); (b) window width was set at 40 milliseconds (between 40 and 80 milliseconds) (a modified window with gradually sloping limits [Figure 2] was used to minimize the artifact that can occur at the edges of the

window when it ends abruptly); (c) the center of the window was defined using the average P50 latency (57.6 milliseconds); and (d) the maximum latency shift allowed for each trial was defined to minimize the possible contribution of other proximal EP waves, P30 and N100 (± 10 milliseconds). (6) For both S1 and S2 and for each trial, the FFT of the filtered then windowed trial was obtained. (7) The FFT of the filtered windowed template was multiplied by the complex conjugate of the FFT of the filtered, windowed trial. (8) The inverse FFT of the product, which is the cross-covariance function, was found. (9) The shift with the maximum cross-covariance within the allowed range of shifts was found. (10) The trial was shifted, and the result was added into the new average. (11) This process was continued for all trials. The average of all the shifted trials was the result for the first iteration of the procedure and became the new template for the next iteration. In the application used herein, no more than 5 iterations of the single-trial procedure were performed.

STATISTICAL ANALYSIS

The effects of the FDAF procedure were tested within each group using repeated-measures analysis of variance (click \times iteration). Analysis of variance also was used to test differences between normal controls and patients with schizophrenia in the average P50 response before (group \times click) and after (group \times click \times iteration) latency correction, and in the S2/S1 ratio measure (group \times iteration). Post hoc comparisons were conducted using the Newman-Keuls method.⁵⁴ Significance levels were set at $P \leq .05$.

N7) (Figure 3). For these 2 controls, using a 40- to 62-Hz bandpass maximized the efficiency of the FDAF procedure (Figure 5).

For both the normal controls ($F_{5,45} = 11.74$; $P < .001$) and the patients with schizophrenia ($F_{5,45} = 34.06$; $P < .001$), P50 amplitude was significantly enhanced after latency adjustment. Post hoc comparisons showed that, for both groups, there was no further significant change after the first iteration of the FDAF (Figure 6).

COMPARISON OF SCHIZOPHRENIC PATIENTS AND CONTROLS

Analysis of temporal variability over single trials (the SD of the average temporal shift required to optimally align the single trials with the template) between the groups revealed a significant main effect of iteration ($F_{4,72} = 19.72$; $P < .001$). A main effect for click ($F_{1,18} = 3.93$; $P = .06$) and a group \times click interaction ($F_{1,18} = 3.73$; $P = .07$) did not reach significance. A significant group \times click \times iteration interaction ($F_{4,72} = 3.23$; $P = .02$) showed that temporal variability was larger for patients with schizophrenia than for controls for P50 to S1 but not to S2 (Table). Post hoc comparisons showed that this was the case for each iteration of the FDAF for S1.

Before the average P50 was corrected for temporal variability, there was a significant difference between the

patients with schizophrenia and normal controls in P50 peak-to-peak amplitude to S1 but not to S2 (group \times click interaction, $F_{1,18} = 8.79$; $P = .01$). After latency adjustment, this interaction was not significant (Table) (Figure 6), and a main effect for click showed that P50 amplitude to S1 was larger than to S2 for both groups ($F_{1,18} = 6.30$; $P = .02$).

One subject with schizophrenia (S3) had an average P50 amplitude of 0.0 to S1 and was eliminated from the statistical analysis comparing the gating ratio in patients with schizophrenia and normal controls before and after latency adjustment. A significant ratio \times iteration interaction ($F_{1,18} = 4.78$; $P = .04$) showed that the gating ratio before latency adjustment was larger in patients with schizophrenia than in controls. After latency adjustment (fifth iteration) this difference was no longer significant (Table).

SIGNAL-TO-NOISE RATIO

To obtain an index of the effectiveness of the FDAF, the cross-covariances between each point in the template and the single trial, used to derive the temporal shift required to form the latency corrected averages, were transformed into cross-correlations by dividing by the appropriate SDs. For the filtered, windowed data, the average cross-correlations between the template and single tri-

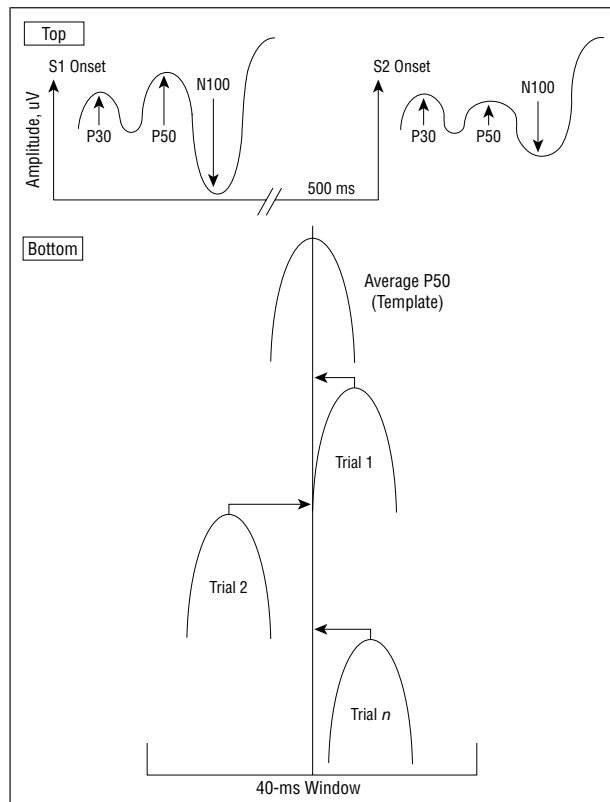


Figure 1. Top, Idealized auditory evoked potentials in the dual-click S1, S2 paradigm, with the P30, P50, and N100 waves (named for their approximate latency from stimulus onset) indicated by arrows. The timeline is not to scale. Bottom, The single-trial procedure. The template, or average P50 over trials, is shown at the top, with successive single trials shown below. The vertical line marks the point at which, in this idealized example, the maximum point by point cross-correlation between the template and single trial would be achieved. The arrows above each single trial illustrate the latency shift required to reach the maximum correlation and indicate the amount each trial would have to be shifted to form the latency-corrected average.

als were calculated before the FDAF procedure and for each successive iteration. Before the FDAF, for the normal controls the average correlations were 0.52 and 0.39 for S1 and S2, respectively, and for the individuals with schizophrenia the correlations were 0.41 and 0.38. After the FDAF, the correlations improved significantly ($F_{5,90} = 113.14$; $P < .001$), ranging between 0.70 and 0.76, and did not differ significantly between the groups.

COMMENT

This study demonstrated a single-trial analysis method that can be used to study fluctuations in the timing of the P50 EP in schizophrenia. The single-trial correlational template method (Figure 1) has been successfully used to study the contribution of temporal variability to the later and larger N100, P200, and P300 components,⁴⁰⁻⁴² but there has been skepticism regarding the use of this method to resolve the single-trial P50 component.²⁵ Our findings confirmed, using an automated, objective procedure, that temporal variability can contribute significantly to the P50 response in the gating procedure, as reported in our earlier article.²⁴

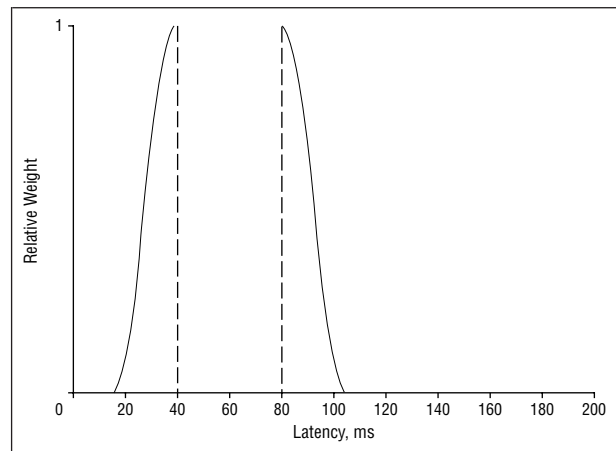


Figure 2. The modified Hanning window used in our frequency domain adaptive filter procedure to set the expected temporal range of P50 (40-80 milliseconds). Note that the edges of the window do not end abruptly, but gradually slope toward 0.

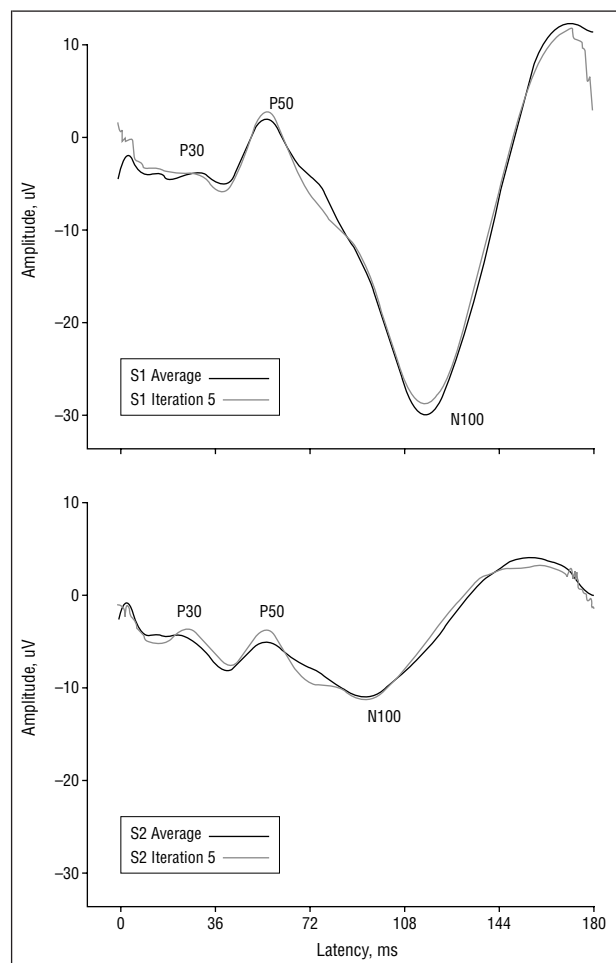


Figure 3. Averaged evoked responses to S1 (top) and S2 (bottom) before (solid black line) and after (solid gray line) latency adjustment (fifth iteration) for 1 normal control.

In agreement with earlier studies showing increased EP variability in schizophrenia,^{26-37,39,40} P50 single-trial temporal variability to S1 was larger in patients with schizophrenia than in normal controls. Also in support of our findings, Schwarzkopf et al⁵⁵ observed that their

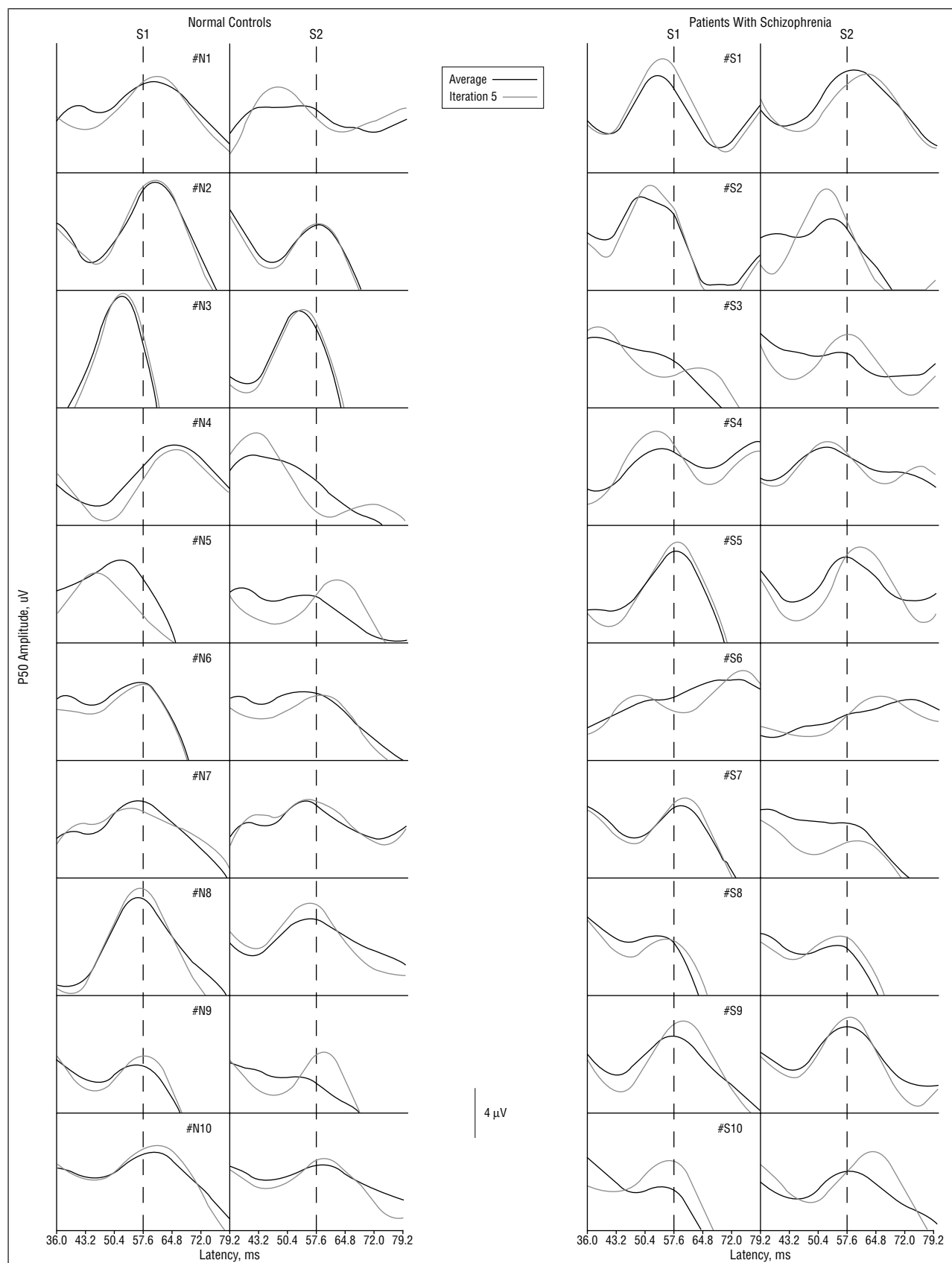


Figure 4. Averaged P50 evoked responses to S1 and S2 before latency adjustment (solid black line) and after the fifth iteration of the frequency domain adaptive filter procedure (solid gray line) for normal controls ($n = 10$) (left) and patients with schizophrenia ($n = 10$) (right) using the 25- to 62-Hz bandpass. The broken line at 57.6 milliseconds shows the approximate location of P50 for each subject.

P50 suppression measure showed low-rank order stability over the testing period, and this measure of variability was significantly greater in patients with schizophrenia than controls.⁵⁶ They concluded that the variability in P50 suppression might itself be an informative measure of central inhibitory mechanisms. The precise neurophysiological mechanism for the increased temporal variability we observed in patients with schizophrenia is not known, but it may reflect a neurophysiological sensory input processing deficit resulting from a hyperactive nervous system, in which erratic neuronal firing affects the generation of the P50 to both S1 and S2. Moreover, P50 suppression is not consistently found in normal controls,⁵⁷ and individual differences in temporal variability may contribute to these inconsistent findings.

The findings of this study using the FDAF procedure supported the results of Jin et al²⁴ that correction for temporal variability eliminated the significance of the difference between normal controls and patients with schizophrenia in P50 amplitude to S1 and the P50 gating ratio. The finding that P50 average amplitude to S1 is decreased in patients with schizophrenia has been reported by a number of the investigators who originally reported larger S2/S1 ratios and impaired sensory gating in schizophrenia.^{8-10,19,22,23} Several of these investiga-

tors have proposed that dopamine-induced neuronal hyperresponsivity could lead to decreased synchrony in the response to auditory input and the observed decrease in P50 amplitude.^{8-10,19} An hypothesis of desynchronized neuronal activity also may be a mechanism underlying the effect of EP variability on the amplitude of S1 in the schizo-

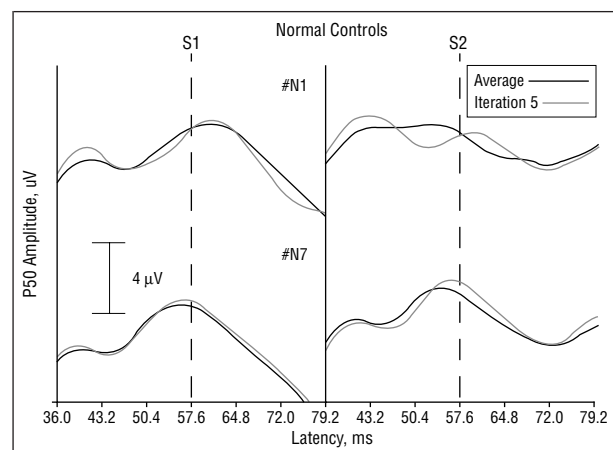


Figure 5. Averaged P50 evoked responses to S1 and S2 before latency adjustment (solid black line) and after the fifth iteration of the frequency domain adaptive filter procedure (solid gray line) for 2 normal controls using the 40- to 62-Hz bandpass. The broken line at 57.6 milliseconds shows the approximate location of P50 for each subject. For subject N1, using this higher bandpass allowed the separation of P30 and P50, and for subject N7, using the 40- to 62-Hz bandpass resulted in an enhancement of P50 that was not seen using the 25- to 62-Hz bandpass (compare with Figure 2).

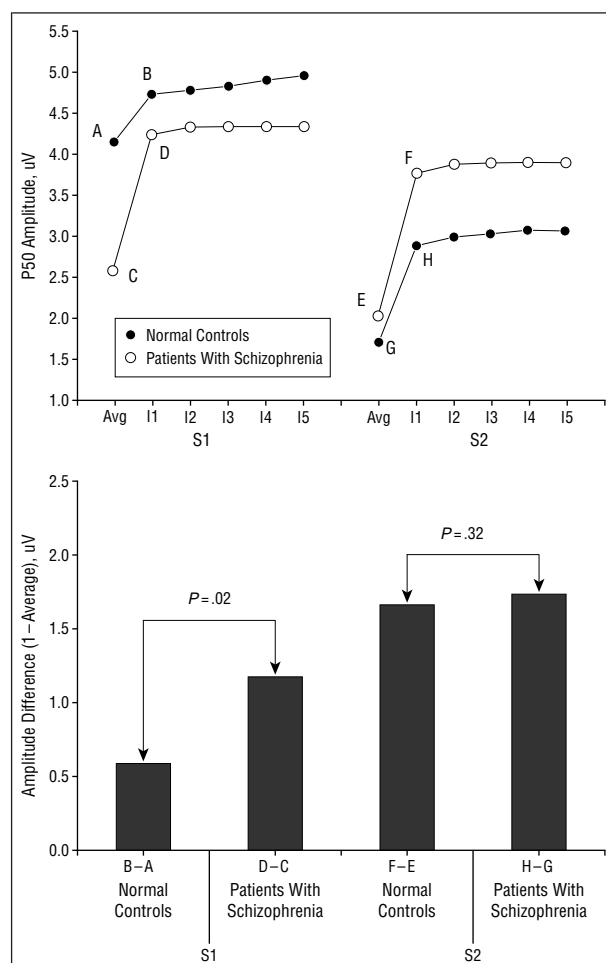


Figure 6. Average P50 amplitude to S1 and S2 before latency adjustment and after each iteration (I) of the frequency domain adaptive filter procedure (top). The difference between points A and B was significant (average P50 amplitude to S1 before latency adjustment in normal controls [$n = 10$] compared with patients with schizophrenia [$n = 10$]), but the difference between points C and D was not (average P50 amplitude to S1 after latency adjustment). The bar graph (bottom) shows that the S1 amplitude increase after the frequency domain adaptive filter procedure was larger in patients with schizophrenia than in normal controls, but for S2, there was no difference between the groups in the amount P50 increased after latency adjustment.

Mean P50 Amplitudes, SD of Shifts for S1 and S2, and S2/S1 Ratios for Normal Controls ($n = 10$) and Patients With Schizophrenia ($n = 10$)*

Group	Click	P50 Amplitude, μ V		SD of Shifts		S2/S1 Ratio	
		Average	Iteration 5	Iteration 1	Iteration 5	Average	Iteration 5
Normal controls	S1	4.14 (0.85)	4.95 (0.90)	4.04 (0.46)	4.69 (0.55)	0.36 (0.08)	0.74 (0.11)
	S2	1.71 (0.61)	3.08 (0.56)	5.02 (0.51)	5.70 (0.61)		
Patients with schizophrenia	S1	2.57 (0.57)	4.33 (0.71)	4.84 (0.35)	5.60 (0.38)	1.18 (0.47)	0.88 (0.14)
	S2	2.03 (0.52)	3.92 (0.63)	5.08 (0.36)	5.49 (0.40)		

* Values are mean (SE).

phrenic group reported in this study. For example, neuronal synchrony can be affected when the rate of background firing is too high, which can be caused by an imbalance between excitatory and inhibitory tone.⁵⁸

Latency adjustment enhanced P50 amplitude for both normal controls and patients with schizophrenia, but, as Figure 3 illustrates, the degree of enhancement varied considerably among individual subjects, suggesting that the degree of neuronal synchrony of the P50 response to each stimulus varies among subjects as well as between patients with schizophrenia and controls. The necessity to use a higher bandpass (40-62 Hz) for 2 normal controls to obtain a clear separation between P30 and P50 illustrates that individual differences in the frequency range of the P50 response can affect the outcome of the procedure and should be taken into account when the procedure is applied. (When these 2 normal controls were eliminated from the analysis, the statistical differences between normal controls and patients with schizophrenia described in the results still were observed.)

The question of signal-to-noise ratio is an important consideration in the application of the FDAF procedure, especially when the signal of interest is small. Several steps were taken to reduce the likelihood that the procedure would amplify noise instead of P50: (1) The electroencephalogram was prefiltered to exclude high-frequency activity above 80 Hz unrelated to the signal (low-frequency activity would require a window larger than 40 milliseconds to be included). (2) The bandpass filter was selected to include activity in the range of P50 (25-62 Hz). (3) Trials with major artifact were automatically excluded. (4) The maximum allowed shift minimized the possibility that P30 would be selected. The average correlation between the average EP (the template) and the single trials is assumed to reflect the signal-to-noise ratio, such that higher correlations result in the more reliable detection of the signal.⁵⁹ These correlations rose significantly after the FDAF procedure (all above 0.70) and characterized both patients with schizophrenia and controls.

The effectiveness of the 25- to 62-Hz bandpass filter in this study supports evidence that the P50 component is a 40-Hz (gamma band) response, placing it in the context of fundamental electroencephalographic phenomena. Basar and colleagues^{53,60-62} used single-trial analysis and bandpass filtering to study the relationships between the electroencephalogram and EPs and to test their theory that EPs reflect the temporal synchronization of the electroencephalogram to an external event.⁶⁰⁻⁶² Using these methods and in agreement with our findings, Basar et al⁵³ showed that activity in the 40-Hz range contributes significantly to the formation of the P50 peak of the auditory evoked response as well as to P30. More recently, Clementz et al⁶³ also obtained data consistent with an hypothesis that P50 is a subcomponent of the 40-Hz response. Transient synchronous neuronal gamma oscillations have been observed in many cortical neural networks and over large distances and are thought to underlie effective neuronal communication and binding of perceptual features.^{64,65} Techniques such as single-trial analysis make it possible to study the dynamic properties of brain activity, which can be lost with conventional averaging methods.^{53,60-62,66}

In contrast to the proposition that the P50 gating deficit is strictly a neurophysiological deficit,^{8,10,11,67-69} recent studies have shown that P50 amplitudes can be affected by attentional manipulations and that the effects of attention on P50 can reduce or reverse findings of P50 suppression at S2.⁷⁰ Moreover, measures of P50 gating were correlated with measures of sustained attention in schizophrenia.¹⁹ These findings could suggest that a deficit in inhibitory function could underlie behavioral expressions of attentional problems¹⁹ and/or that early components of the EP are affected by attention.⁷⁰ If P50 is affected by attention, it could be predicted that fluctuations in attention from trial to trial would be greater in patients with schizophrenia than in normal controls, leading to greater temporal variability in the P50 response. Our results suggest that temporal variability may be a central feature underlying deficits in attention and cognition in schizophrenia.

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