Poor P50 Suppression Among Schizophrenia Patients and Their First-Degree Biological Relatives

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Objective: This study's goal was to replicate the finding that family members of schizophrenia patients show poor P50 suppression during a paired-click auditory evoked response paradigm. **Method:** The paired-click paradigm was used to test 44 schizophrenia patients, 60 of their clinically unaffected first-degree relatives, and 45 normal subjects. Two clicks (83 dB[A] over a 60-dB[A] white noise background) separated by 500 msec were presented 60 times to all subjects. P50 responses to the first and second clicks were selected from the digitally filtered data by using standard methods and the Cz recording site. **Results:** The schizophrenia patients had smaller P50 responses to click 1 than either their relatives or the normal subjects; the patients and their relatives, who did not significantly differ, had larger P50 responses to click 2 than the normal subjects. Schizophrenia patients had worse P50 suppression than either their family members or the normal subjects; the patients' family members had worse P50 suppression than the normal subjects. **Conclusions:** Family members of schizophrenia patients have worse P50 suppression than normal subjects. To the authors' knowledge, this is the first demonstration independent of the group associated with the University of Colorado that schizophrenia patients' family members have poor P50 suppression. This result is intrinsically important, perhaps especially because a recent report suggests genetic linkage of poor P50 suppression to the cholinergic receptor's α_7 nicotinic subunit.

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Normal subjects show suppression of the 50-msec auditory evoked response (P50) to the second of two clicks when these clicks are presented about 500 msec apart. Typically, normal subjects show about 60%–80% suppression of the P50 amplitude for the second click in relation to the first click. Schizophrenia patients have shown a relatively larger P50 response to click 2 in a paired-click auditory evoked response paradigm, resulting in only 20%–50% suppression (1–7). Poor P50 suppression is theoretically related to defective inhibition and an associated vulnerability to sensory overload and cognitive fragmentation (8). A proportion of schizophrenia patients' clinically unaffected first-degree biological relatives (i.e., those without schizophrenia themselves) also have poor P50 suppression, suggesting that this measure may be associated with genetic liability for this illness (9, 10). Recently, Freedman and colleagues (11) reported genetic linkage between poor P50 suppression and the cholinergic receptor's α_7 nicotinic subunit.

The basic P50 suppression effect among schizophrenia patients has been replicated numerous times by independent laboratories; however, only the group associated with the University of Colorado has demonstrated that a subset of schizophrenia patients' clinically unaffected relatives have poor P50 suppression. For a measure to be useful as a biological marker in family and linkage studies, it should be repeatable and capable of being studied by independent laboratories (see, e.g., reference 12). Our aim for the present study was to determine whether we could replicate the finding of poor P50 suppression among unaffected first-degree biological relatives of schizophrenia patients as a prelude to performing linkage studies.

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METHOD

Subjects

All subjects were evaluated clinically by using diagnoses based on the Structured Clinical Interview for DSM-III-R (SCID), modules A-

TABLE 1. Mean Values for P50 Variables During Paired-Click Auditory Evoked Response Paradigm[a] for 44 Schizophrenia Patients, 60 of Their Clinically Unaffected First-Degree Biological Relatives, and 45 Normal Subjects

	Schizophrenia Patients		Relatives of Schizophrenia Patients		Normal Subjects	
P50 Variable	Mean	SD	Mean	SD	Mean	SD
Click 1 latency (msec)	61.3	4.1	61.4	3.7	62.2	3.3
Click 2 latency (msec)	58.0	11.4	57.8	11.7	57.7	12.1
Click 1 amplitude (μV)	3.35	1.14	3.92	1.51	4.16	1.20
Click 2 amplitude (μV)	1.88	0.92	1.78	1.18	1.21	0.97
% suppression ratio	40.6	31.6	52.2	30.3	70.1	22.8
Difference score	1.47	1.13	2.14	1.55	2.95	1.34

[a] Two clicks (83 dB[A] over a 60-dB[A] white noise background) separated by 500 msec were presented 60 times. The P50 suppression ratio is the percent decrease of the P50 amplitude for click 2 from the click 1 amplitude. The difference score is the click 1 amplitude minus the click 2 amplitude.

E (13). The participants were in good physical health, had no known neurological hard signs, and were free of current psychoactive substance use disorders. All participants provided written informed consent before testing.

Patients with schizophrenia were recruited from inpatient and outpatient facilities associated with the University of California at San Diego, local newspaper advertisements, and local chapters of the Alliance for the Mentally Ill. The 44 patients had a DSM-III-R diagnosis of schizophrenia and a median score on the Global Assessment of Functioning scale of 30 (25th–75th percentiles=25–37). Their mean age was 34.2 years (SD=9.3), and 18% were female (N=8). At the time of testing, 31 patients were receiving antipsychotic medication (median chlorpromazine-equivalent dose=347 mg/day, 25th–75th percentiles=0–535); 31 patients were also receiving anticholinergic medications.

From 20 families we recruited 60 first-degree biological relatives of the schizophrenia patients, 29 of whom were parents of the probands. The relatives' mean age was 43.6 years (SD=16.7), and 50% were female (N=30). According to Weinberg's abridged method (14), the morbid risk for schizophrenia in this group of first-degree relatives was 2.3% (SD=2.2%) (one case of schizophrenia; this subject was included in the schizophrenia group for subsequent analyses). This rate is lower than the 6.5% (SD=1.6%) reported by Kendler and colleagues (15). This discrepancy was not surprising since our study was not epidemiological, and some of the affected family members were unavailable for study because of hospitalization, head injuries, or unwillingness to participate. The remaining relatives were free of psychotic disorders. Eleven of the relatives also met the criteria for major depression (six of whom had current symptoms).

We recruited 45 normal subjects through local advertisements (e.g., campus, golf club, grocery store, and fitness center bulletin boards; newspaper listings); their mean age was 34.6 years (SD=14.6), and 56% were female (N=25). These subjects were screened for a history of psychiatric disorder among their first-degree biological relatives. Only subjects without a major affective disorder, psychotic disorder, or current psychoactive substance use disorder who did not have a family history of psychotic disorder, suicide, or psychiatric hospitalization were asked to participate.

Apparatus and Procedure

Data were collected by using a Grass Model 12 Neurodata Acquisition System (Quincy, Mass.) and a customized San Diego Instruments SR-LAB startle response monitor (San Diego). EEG was recorded from the Cz site by using a tin electrode referenced to linked earlobe electrodes (Electro-Cap International, Inc., Eaton, Ohio). The ground was placed at the middle of the forehead. Eye movements were recorded by means of electro-oculography (EOG) with Ag-AgCl electrodes placed at the outer canthus and below the right eye. Electrode impedances were below 10 kΩ. The subjects were seated in a comfortable reclining chair and wore Maico TDH-39P headphones (Minneapolis) for auditory stimulus presentations.

The ambient sound pressure level of the testing room was 55 dB(A). To provide control over the background sound pressure level during stimulus presentation, 60-dB white noise was presented continuously over the headphones throughout testing. The subjects were told to close their eyes, relax, sit still, but not fall asleep for several minutes. They were also told that they would hear clicks over the headphones and that they should pay attention to these clicks when they occurred. There was a 3-minute acclimation period (white noise only) before the initiation of stimulus presentation.

The EEG and EOG were recorded by using analogue 1.0-Hz high-pass and 300-Hz low-pass filters (–3 dB) and were sampled by using a 12-bit A-D converter at 1000 Hz. Calibration pulses were recorded for each subject before testing. For all subjects, the A-D resolution for both the EEG and EOG was between 17 and 20 digital units per microvolt.

The SR-LAB system generated a flat broadband (250 Hz to 50 kHz) square wave of 1-msec duration (rise time of 12–15 μsec) that was delivered through the headphones (bandwidth of resulting output approximately 300 Hz to 18 kHz). The average intensity of the resulting click was 83 dB(A). The clicks were presented in pairs separated by 500 msec. The intertrial interval varied pseudorandomly between 6 and 10 sec (average=8 sec). Sixty pairs of clicks were presented to all subjects, and the digitized data were stored for later off-line analyses. The data acquisition time was from 100 msec before to 400 msec after each click.

Signal Processing and Response Scoring

Signal processing and scoring of evoked responses were performed off-line by raters blind to group membership. We used a series of two digital filters for processing the EEG before selection of P50 peaks and calculation of P50 suppression: 1) a 7-point moving average and 2) Coppola's successive difference high-pass filter (16) (filter parameter A=0.95). They were applied twice, once in each direction, to the individual trials. The EOG was also filtered on a trial-by-trial basis by using a 7-point moving average (also applied twice).

A trial was rejected if there was electrical activity greater than 50 μV in either the EEG or EOG channels between 0 and 100 msec poststimulus. On the basis of visual inspection, trials with prominent alpha- or delta-wave activity, a prominent P30 wave, muscle/ocular artifact in the 0–100-msec poststimulus interval, or absence of a positive-going wave in the P50 interval for click 1 were also excluded (2; 17, pp. 609–610).

If an individual trial's click 1 response was accepted, the EEG and EOG data for the click 2 response were inspected visually. The click 2 response was also accepted unless there was electrical activity greater than 50 μV in either the EEG or EOG channels between 0 and 100 msec poststimulus, or muscle/ocular artifacts in the 0–100-msec poststimulus interval. Only trials with both click 1 and click 2 responses were used in subsequent analyses.

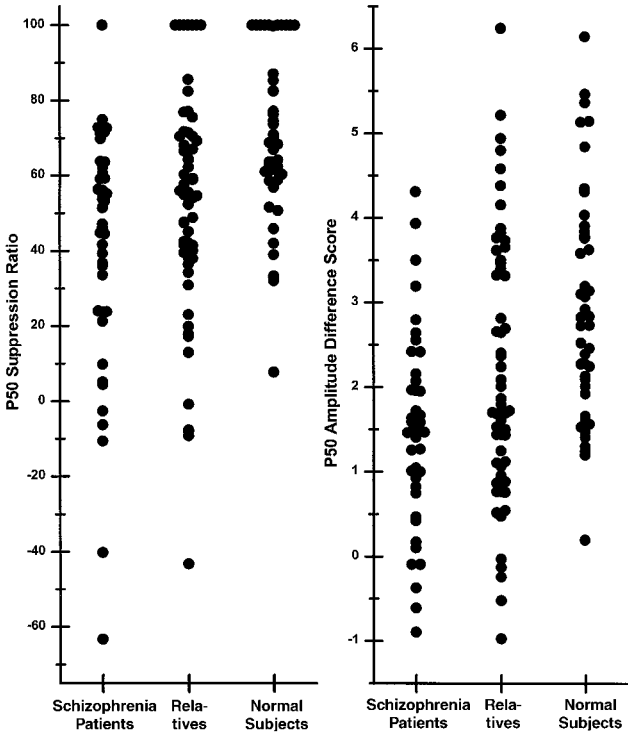
The grand average waveforms for the click 1 and click 2 responses for each subject were presented simultaneously on a high-resolution color monitor. For the click 1 response, the most prominent peak in the 40–80-msec poststimulus window was selected as the P50 peak. The preceding negative trough was used to calculate the P50 amplitude (figure 1 in reference 1). In accordance with the method of Judd and colleagues (5), this trough could not occur less than 30 msec poststimulus (i.e., the trough search was stopped if a horizontal tangent line was not encountered by 30 msec poststimulus, and the 30-

msec point was then used as the start of the P50). By visual inspection of the click 2 response grand average, the positive peak with a latency closest to that of the click 1 P50 peak was selected as the click 2 P50 response. The click 2 P50 amplitude was determined in the same way as for the click 1 response. P50 suppression was quantified in two ways: 1) the percent decrease of the P50 amplitude for click 2 from the click 1 amplitude (P50 suppression ratio) and 2) the difference between the click 1 amplitude and the click 2 amplitude (difference score resulting from click 1 minus click 2) (1, 2, 18).

RESULTS

There were no significant associations between the P50 variables and either age or medication status; therefore, the latter variables were not considered further. The relatives with and without major depressive disorder also did not differ significantly on any P50 variable ($t<1.68$ in all cases), so the relatives were considered as a group in subsequent analyses. To evaluate for differences on P50 variables among the schizophrenia patients, relatives, and normal subjects (table 1), we used group-by-gender analyses of variance. For the click 1 P50 amplitude, there were significant main effects of group ($F=4.60$, df=2, 146, $p=0.01$) and gender ($F=5.49$, df=1, 147, $p=0.02$). The schizophrenia patients had smaller click 1 amplitudes than the relative and normal groups, who did not differ significantly, and the women had larger click 1 amplitudes (mean=4.22 μV, SD=1.25) than the men (mean=3.53 μV, SD=1.35). For the click 2 P50 amplitude, there was a significant main effect of group ($F=5.34$, df=2, 146, $p=0.006$). The schizophrenia patients and their relatives, who did not differ significantly, had larger click 2 amplitudes than the normal subjects. For the P50 suppression measures, there were significant main effects of group on both the suppression ratio ($F=11.85$, df=2, 146, $p<0.001$) and the amplitude difference score ($F=13.08$, df=2, 146, $p<0.001$) (table 1, figure 1). For both measures, the schizophrenia patients had worse suppression than their relatives, and the relatives had worse suppression than the normal subjects.

FIGURE 1. Individual Measures of P50 Suppression During Paired-Click Auditory Evoked Response Paradigm[a] for 44 Schizophrenia Patients, 60 of Their Clinically Unaffected First-Degree Biological Relatives, and 45 Normal Subjects



[a] Two clicks (83 dB[A] over a 60-dB[A] white noise background) separated by 500 msec were presented 60 times. The P50 suppression ratio is the percent decrease of the P50 amplitude for click 2 from the click 1 amplitude. The difference score is the click 1 amplitude minus the click 2 amplitude.

DISCUSSION

This study replicates the finding that schizophrenia patients have worse P50 suppression than their relatives and normal subjects. Most important, relatives of schizophrenia patients had worse P50 suppression than normal subjects whether this variable was quantified by either ratio or amplitude difference score. To our knowledge, this is the first independent demonstration that poor P50 suppression, widely reported among schizophrenia patients (4, 5), is also evident among patients' clinically unaffected first-degree biological relatives. The finding that poor P50 suppression may be an indicator of liability for schizophrenia is important given Freedman and colleagues' recent suggestion (11) of genetic linkage between deficient P50 suppression and the α_7 subunit of the nicotinic receptor. Further work is needed to identify the mechanisms mediating poor P50 suppression among schizophrenia subjects, to clarify how the clinically unaffected relatives of schizophrenia patients could manifest the same abnormality as the patients themselves, and to determine how studies of P50 suppression can inform research on schizophrenia genetics.

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