Effects of P50 temporal variability on sensory gating in schizophrenia

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Received 18 July 1996; revised 5 February 1997; accepted 26 February 1997

Abstract

The conditioning-testing (S1-S2) P50 auditory evoked potential (EP) has been well-documented and accepted as an important tool for measuring sensory gating in schizophrenia research. However, the physiological mechanism of the phenomenon is not known. In this study a single-trial analysis was used to determine the influence of the latency variability of the responses in the formation of the averaged P50. Ten schizophrenic patients and 10 normal controls were tested in the dual-click EP paradigm. Using ensemble averaging analysis, we replicated the previous finding of a lower S1 P50 amplitude and higher S2/S1 ratio in schizophrenics compared with normal controls. The single-trial analysis revealed that patients had significantly higher trial-to-trial latency variability in S1 responses than normal subjects, while the S2 showed the same variability as in controls. Measured by the single-trial procedure, the arithmetic mean amplitudes of P50 responses to S1 and S2 were similar between normal and schizophrenic subjects. The same measure also eliminated the difference in averaged P50 amplitude between S1 and S2 for both groups. Temporal variability appears to be an important factor in the assessment of averaged EPs and thus contribute to the change of P50 amplitude observed in schizophrenia. © 1997 Elsevier Science Ireland Ltd.

Keywords: P50; Latency; Variability; Jitter; Schizophrenia; Gating

1A portion of the study was presented by Dr. Jin at the 49th Society of Biological Psychiatry Annual Convention and Scientific Program at Sheraton Society Hill Hotel, Philadelphia, PA, May 18-22, 1994.

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PII S0165-1781(97)03091-6
1. Introduction

Changes in the auditory P50 evoked potential (EP) in schizophrenic patients have been well accepted as one of the electrophysiological indices of sensory gating abnormalities in schizophrenia (Adler et al., 1982, 1985; Freedman et al., 1983, 1987; Franks et al., 1983; Siegel et al., 1984; Baker et al., 1987, 1990; Boutros et al., 1993). The P50 is a small positive peak in the EEG occurring about 50 ms after a stimulus. To measure the gating effect with P50 responses, a train of paired clicks S1-S2 in a conditioning-testing paradigm is presented, with a 0.5-s intrapair interval and a 10-s interval between pairs. In normal subjects, the time-locked average of the P50 amplitude to S2 is considerably attenuated relative to the S1 response. This is interpreted as evidence of auditory sensory gating, in which S1 activates an inhibitory system that reduces the amplitude of the response to S2 (Adler et al., 1982). The conditioning-testing ratio (the amplitude of the testing response, S2, divided by the amplitude of the conditioning response, S1) has been used as an index of sensory gating capacity. Compared to normal subjects, patients with schizophrenia have an increased S2/S1 ratio (Adler et al., 1982; Freedman et al., 1983, 1987; Nagamoto et al., 1989). This increased S2/S1 ratio is believed to be a biological marker (Freedman et al., 1983) of a fixed trait in schizophrenia and suggested to reflect the primary sensory gating impairment of the disease process.

Although the finding of P50 change in schizophrenics has been well replicated in the literature of psychiatric research, the mechanism underlying the gating phenomenon remains unresolved. The gating deficit observed in schizophrenia commonly has been defined as a failure in the inhibition of the P50 response to S2. However, recent data showed a significant gender difference in the P50 response in normal subjects (Hetrick et al., 1996). Other studies demonstrated that a reduction in the initial P50 response to S1 appears to be an important contributor to the increased S2/S1 ratio (Jin and Potkin, 1996; Adler et al., 1982, 1986, 1988; Freedman et al., 1987; Schwarzkopf et al., 1993; Cullum et al., 1993; Judd et al., 1992). Since the amplitude is evaluated by time-locked averaging, as is true for other EP components (Patterson et al., 1988), the effect of temporal variability (jitter) on the averaged value of P50 amplitude should be taken into consideration (Jin et al., 1994, 1995). Trial-to-trial variability in the P50 response could reduce the averaged S1 amplitude and contribute to the observation of a gating deficit in schizophrenia. Therefore, an assessment of the EP latency for each trial (as opposed to the conventional ensemble average) is needed to explore this possible mechanism of the P50 gating phenomenon.

Early studies used cross-correlation techniques to examine the variability (Shagass et al., 1979; Rappaport et al., 1975; Saletu et al., 1971; Saletu, 1977; Calloway et al., 1970; Inderbitzen et al., 1970; Jones and Calloway, 1970) of various epochs of the EP in schizophrenia. These studies have consistently shown that schizophrenics have higher variation than controls. Shagass et al. (1979) interpreted the finding of increased variability as supporting an impairment of a central filtering mechanism in the schizophrenics which, if functioning normally, would facilitate later processing of sensory input. Inderbitzen et al. (1970) and Rappaport et al. (1975) found that the high variability of the visual EP in schizophrenics was correlated with performance variability on perceptual tasks, and with overall thought disturbance.

More recent studies using the correlational-template procedure have supported the early reports of reduced evoked potential amplitudes and increased variability in schizophrenia in later components of the EP (Ford et al., 1994; Pfefferbaum et al., 1984; Roth et al., 1980). However, both Ford et al. (1994) and Roth et al. (1980) found that, for P300, the amplitude difference between schizophrenic patients and controls was not eliminated when the temporal variability of P300 was corrected by aligning single-trials according to the EP latency, suggesting that the amplitude reduction of later components observed in schizophrenia was not entirely a result of latency variability, but also was indicative of an
overall amplitude reduction in the responses of schizophrenics. In contrast, for the P100 component of the visual EP, temporal variability has been found to be an important factor influencing amplitude in a group of normal controls (Rosenstein et al., 1994). The present study was designed to assess the degree of temporal variability in the P50 response over single trials in both normal and schizophrenic subjects, and to evaluate the influence of this variability on averaged P50 amplitudes as well as the gating ratio.

2. Materials and methods

2.1. Subjects

Ten schizophrenic patients (4 females, 6 males, age: $33.1 \pm 7.6$) and 10 normal healthy volunteers (6 females, 4 males, age: $26.5 \pm 3.5$; $t = 1.90$, d.f. = 9, n.s.) who had given informed consent were tested. Diagnosis was made by two independent research psychiatrists according to DSM-III-R criteria for schizophrenia. All patients were free of medication for at least 5 days at the time of the study. Normal subjects were screened by a questionnaire and interviewed by a psychiatrist to ascertain the absence of a personal and familial history of mental illness, or personal illicit drug use.

2.2. Procedure

During the test, subjects were seated in a comfortable recliner in an acoustically and electrically shielded dark room. They were instructed to relax with their eyes closed. A series of paired clicks (S1 and S2) separated by 500 ms were presented at 10-s interpair intervals through a set of headphones. Clicks were triggered by an acoustic stimulator (Nihon Kohden Model SSS-3200) interfaced to a Neurodata Inc. EEG system. The intensity of the clicks was adjusted to 100 dB SPL.

Evoked potential signals were collected from Ag-AgCl cup electrodes placed using adhesive paste at the vertex (Cz) and referenced to linked mastoids. EEG trials contaminated by major artifacts ($\pm 75 \mu V$) were automatically rejected by a threshold filter. Forty 180-ms EEG epochs, band-pass filtered at 0.56–500 Hz, were then sampled by a 16-bit A/D converter at the rate of 2756 points/s for each trial. The electrooculogram (EOG) was recorded to eliminate trials contaminated by eye movement and blinking. These artifact-free epochs were then averaged on-line by a computer (Neurodata Inc.). The averaged and the raw data were saved on hard disk for further off-line single-trial analysis.

In the single-trial EP analysis, a digital approximation of a Butterworth filter was used to reduce the noise (DeFatta et al., 1988). The optimal frequency window for the filter was determined according to the averaged EP (Suzuki et al., 1983). The filter selected (8–60 Hz) was applied to the single-trial analysis. In order to avoid phase distortion, each trial was filtered twice, first in the forward direction and then in reverse (Signal Processing Toolbox User’s Guide, 1988). Each filtered trial was also visually inspected to further reject movement artifact before entering the measurement. Any case with four or more rejected trials on the basis of this visual inspection procedure was excluded from further analysis. Consistent with previous studies using time-locked averaging (Adler et al., 1982; Freedman et al., 1983, 1987), the peak of the filtered single-trial P50 was determined as the most positive deflection within the range of 40–80 ms after click onset. The amplitude of P50 was defined as the absolute difference between the positive peak within the specified window and the preceding negative trough. The latency was measured as the time delay to peak onset after the stimulus. According to these criteria, a computer subroutine was composed to automatically measure the amplitude and the latency of each P50 response.

2.3. Statistics

Data are reported as mean ± S.D. Because of the small N and the lack of normality of the data distribution, the group mean differences in both averaged and single-trial P50s were tested by the Mann–Whitney rank sum test, a non-parametric statistic. Within-group comparisons were tested with matched t-tests. Variation coefficients (CV = S.D./mean) were calculated for both latency
and amplitude variabilities to standardize the individual measurement since the standard deviation was affected by the inter-subject variance of the means. The group differences in the means of the CVs were then compared with the Mann-Whitney rank sum test. The relationship between the averaged amplitude and the single trial latency variability was tested with Spearman rank correlations.

3. Results

Consistent with previous studies (Adler et al., 1982; Freedman et al., 1983, 1987), a significant difference in the gating ratio (S2/S1) obtained using time-locked average EPs was found between schizophrenic and normal subjects (P = 0.02, Table 1). The amplitude of the P50 response was reduced at S1 (P = 0.05) but not at S2 (P = 0.91) in schizophrenics compared to controls. Fig. 1 shows the P50 responses (S1, solid line; S2, dotted line) averaged across subjects in normal (A) and schizophrenic (B) groups.

Variation coefficients (CV) were calculated for both amplitude and peak latency to assess the cross-trial variability of the P50. Schizophrenic patients had significantly greater latency variability than normal subjects in S1 P50 (P < 0.001), but not in S2 P50 (P = 0.24; Table 2). Matched t-tests within each group revealed that the latency of P50 to S1 in normal subjects (P < 0.001) but not in schizophrenic patients (P = 0.15). There were no differences in the amplitude variability of P50 between normal and schizophrenic subjects either for S1 (P = 0.88) or S2 (P = 1.00). Amplitude variability of the responses to S1 compared to S2 also did not differ from each other, either in the normal (P = 0.58) or schizophrenic groups (P = 0.56).

In contrast to the results for conventional averaging, when measurement of single trials was used to control latency effect, no group differences were observed in the arithmetic means of S1 amplitudes (P = 0.23) or S2 amplitudes (P = 0.17; Table 3). The mean of the S2/S1 ratios was also found to be similar between schizophrenic and normal individuals (P = 0.55). Moreover, the amplitude difference between S1 and S2 within

![Fig. 1. Grand average EPs in normals (A: N = 10) and schizophrenics (B: N = 10). Compared with schizophrenic patients, normal subjects had higher S1 P50 amplitude (solid line) and lower S2/S1 ratio, while S2 response (dotted line) remained the same between the groups.](image-url)
the subjects was also eliminated with the single-trial analysis, in both normal (P = 0.98) and schizophrenic groups (P = 0.11).

Fig. 2 illustrates individual trials of P50 responses in a normal and a schizophrenic subject, both of whom have the closest P50 value to the mean of their respective groups. Each line represents a filtered single-trial EP. The top panels show that the P50 in the normal subject is very well aligned to the conditioning (S1) stimuli (left panel) but not to the testing (S2) stimuli (right panel), i.e. the latency variability of P50 to S2 is higher than to S1. The bottom panels show that the P50 in the schizophrenic patient is poorly locked in time for both stimuli (left panel, conditioning; right panel, testing), i.e. considerable latency variability to S1 and S2 in schizophrenic subjects. The relationship between P50 averaged amplitude and the single-trial latency variability of the P50 to S1 was analyzed by Spearman correlations. There was a significant inverse correlation between the averaged S1 P50 amplitude and its cross-trial latency variability in normal controls (r = −0.68, P < 0.05) but not in schizophrenic patients (r = 0.28, ns). Normal subjects with greater latency variability had a lower averaged amplitude of P50 response to S1. The correlation between the averaged amplitude of S2 P50 and its cross-trial latency variability did not reach statistical significance in either group.

As a check on the validity of the single-trial procedure to select a signal from noise, two additional normal subjects were tested in two separate sessions with different stimulation conditions. In session 1, subjects were tested with the dual-click stimuli. In session 2, subjects’ EP data were collected when the auditory stimuli were omitted. Data acquisition and other experimental settings were identical between the two tests. The number of peaks identified within the specified P50 time window (40–80 ms) were calculated to compare the differences between the two sessions (Fig. 3). It was found that, in the stimulus condition, only two out of 40 trials (5%) were rejected due to the absence of a positive peak in the P50 time window. In the no-stimulus condition, however, 18 out of 40 trials (45%) were rejected because of the absence of any positive component in the time window. These findings support the argument that the single-trial method is not just selecting noise.

Fig. 4 shows the latency-corrected and the conventionally averaged waveforms of S1 P50 to further demonstrate the latency variation effect on averaging. Waveforms with latency adjustment have similar morphology to the conventional waveforms. The latency-corrected averaged waveforms have significantly increased P50 amplitude compared to the conventional waveforms (Normal: 11.3 ± 5.5 vs. 5.6 ± 2.8, t = 5.29, P < 0.001;...
Schizophrenic: $8.1 \pm 3.8$ vs. $3.3 \pm 1.7$, $t = 4.74$, $P < 0.01$. There is a difference between the arithmetic means of the individually measured single trials (Table 3) and the latency-adjusted averages in amplitudes. This difference is primarily due to the fact that the averaging can still blur the waveform of individual response, particularly the trough proceeding to the P50.

4. Discussion

The results of the present study, using the conventional averaging procedure, showed that the P50 gating ratio was significantly increased in the schizophrenic group compared to controls. This finding agrees with the results of a number of previous studies and is usually interpreted as evidence for impaired sensory gating in schizophrenics (Adler et al., 1982, 1985; Freedman et al., 1983; Siegel et al., 1984; Baker et al., 1987, 1990; Nagamoto et al., 1989; Boutros et al., 1993; Erwin et al., 1991). The failure of sensory gating is hypothesized to lead to an overload of sensory input reaching consciousness (Carr and Wale, 1986; Venables, 1964; McGhie and Chapman, 1961; Shakow, 1963) and to account for deficits in information processing and attention observed in schizophrenia.

In addition to the increased $S2/S1$ ratio, the results of this study showed that the averaged P50 amplitude to $S1$ was significantly reduced in schizophrenics compared to controls, while P50 to $S2$ did not differ between the groups. This latter finding also has been reported in the literature by a number of the investigators who have observed increased $S1/S2$ ratios in schizophrenia (Adler et al., 1982; Freedman et al., 1987; Schwarzkopf et al., 1993; Cullum et al., 1993; Erwin et al., 1991).
These findings suggest that changes in the S1 amplitude may be as important as the amplitude of S2 in determining the size of the gating ratio (Jin and Potkin, 1996). The reduction in amplitude of the S1 P50 in schizophrenic patients could reflect three possible mechanisms: (1) a generalized amplitude attenuation of all single responses; (2) a reduction in some, but not all of the responses, and no temporal variability from trial to trial; or (3) an increase in temporal variability in the responses, such that the amplitudes are not reduced overall, but vary in latency, resulting in a lower amplitude averaged response (Ford et al., 1994). Our findings indicate that, when P50 was measured on a single trial basis, the temporal variability of P50 contributed to the averaged P50 amplitude and, consequently, to the ratio value of S2/S1 used as a measure of sensory gating. In a group comparison, schizophrenic subjects had a significantly higher temporal variability in S1 P50 than normal controls. The two groups did not differ in the latency variability of S2 P50. In normal subjects, the single-trial analysis showed that S2 responses were significantly greater in temporal variability than S1 responses. There was no such variability difference between P50s to S1 and S2 in schizophrenic patients. Furthermore, in normal controls, the single-trial temporal variability was found to be inversely correlated with the averaged amplitude of the EP component. These data indicate that a mechanism underlying the poor gating performance described for schizophrenic patients as a higher ratio of S2/S1 may be an increase in latency variability which results in a smaller averaged peak response to S1. This suggestion is supported by the data from normal
Fig. 4. Comparison of latency-corrected averaged S1 P50s (bold line) with the conventional (light line) averaged waveforms. Normal controls (N = 10) listed in left column; schizophrenic subjects (N = 10), right column. The morphology appears to be the same between the two types of waveforms except that the amplitudes with latency correction are significantly higher than those with conventional averaging.
subjects, which showed that the gating effect in this group (low S2/S1 ratio) was, to a great extent, affected by the increased temporal variability in S2 response, resulting in a lower amplitude with the time-locked averaging. Other investigators noted that the P50 suppression measure was not reliable and showed low rank order stability over the testing period (Cardenas et al., 1993; Smith et al., 1994). This within-session variability was significantly greater in schizophrenics than controls. Similarly, the current data showing a high temporal variability of P50 responses among schizophrenics is also a reflection of increased within-session variability in P50 suppression.

We suggest that the averaged amplitude of P50 to S1 could be indicative of consistency in the initial response to the incoming stimuli. As Adler et al. (1982) explained, when a neuronal population is hyperactive, its constant background discharge makes it less likely that the majority of the neuronal population will respond synchronously to any stimulus. The higher latency variability of the P50 in schizophrenia may reflect a brain state that is activated by other irrelevant inputs, which normally should be filtered. This temporally based phenomenon cannot be measured by the conventional averaged EP.

The finding that temporal variability can lead to a reduction in averaged P50 amplitude thereby influencing the gating ratio does not contradict theories regarding failed sensory gating in schizophrenia, but may itself be a manifestation of the abnormal sensory process. There is evidence that the amplitude of the P50 may reflect central inhibitory processes. Schwarzkopf et al. (1993) observed that P50 amplitude to S1 was significantly correlated with startle inhibition and PPI. They found that P50 amplitude was more consistently correlated with the measures of startle inhibition over the testing session than the measure of P50 suppression. It was suggested that P50 amplitude ‘itself may be an indicator of sensory inhibition’ such that ‘the central mechanisms that lead to enhanced P50 amplitude also result in greater inhibition of startle reactivity’ (Schwarzkopf et al., 1993).

Our results also indicated that the single-trial analysis of P50 was successful at separating signal from noise when stimulus and no-stimulus conditions were compared. Another widely used method for correcting latency variability is a template-matching automated procedure based on the Woody adaptive filter (Wastell, 1977; Arpaia et al., 1989). With this method EP signals can be extracted from noise on a single trial basis, even when the characteristics of the signals are unknown in advance. The procedure is to cross-correlate each data sample with a given ‘template’ (e.g. averaged waveform) at various delays. After identifying the delay with the maximal correlation coefficient, the single EPs are realigned in time before averaging. The signal-to-noise ratio is reflected in this procedure by the correlation between the template and the single-trial EP. The advantage of the current procedure for the purposes of this study was that the waveform of each trial was inspected before entering the analysis. In practice, however, a more efficient and automated analysis package for single-trial data will be useful.

The current study replicated previous results of gating deficits in schizophrenia and introduced evidence that temporal variability may contribute to central inhibitory processes. However, we consider these data preliminary, and future study with a new population of subjects and an automated procedure with false trial rejection is required to confirm this finding.

Acknowledgements

This work was supported in part by a NARSAD Award (to Dr. Jin), FIRST Award MH49237 (to Dr. Jin), NIMH Grant MH53808-01 (to Dr. Potkin), and NIMH MH44188 (to Dr. Bunney). The authors would like to thank Dr. E. Roy John for his helpful comments and discussion.

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