Failures of automatic and strategic processing in schizophrenia: comparisons of event-related brain potential and startle blink modification

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Abstract

Noises elicit startle blinks that are inhibited when immediately (~ 100 ms) preceded by non-startling prepulses, perhaps reflecting automatic sensory gating. Startle blinks are facilitated when preceded by prepulses at longer lead intervals, perhaps reflecting strategic processes. Event-related brain potentials (ERPs) and startle blinks were used to investigate the well-documented prepulse inhibition failure in schizophrenia.

Blinks and ERPs were recorded from 15 schizophrenic men and 20 age-matched controls to noises alone and to noises preceded by prepulses at 120 (PP120), 500 (PP500) and 4000 ms (PP4000) lead intervals. Neither blinks nor any of the ERP components elicited by the noise alone differentiated schizophrenics from controls, although responses to noises were modified by prepulses differently in the two groups. With the N1 component of the ERP, patients showed normal inhibition but lacked facilitation, and with P2, patients lacked inhibition, but showed normal facilitation. With reflex blinks and P300, inhibition was seen in both groups, but no facilitation.

These results suggest that different neural circuits are involved in blink and cortical reflections of startle modification in schizophrenics and controls, with both automatic and strategic processes being impaired in schizophrenia. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Patients with schizophrenia suffer not only from psychotic symptoms that might be explained by sensory processing deficits, perhaps resulting in their susceptibility to information overload and inability to ignore unimportant information. This deficit has been observed in the context of sensory gating experiments. When two events happen within 300 ms of each other, the response to the second event is reduced ('gated' out) to allow priority processing of the first event. If the responsiveness to the second event is not reduced, a deficit in sensory gating may be assumed, and flooding with irrelevant information may result.

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Braff and colleagues (e.g., Perry and Braff, 1994) have suggested that sensory gating failures in schizophrenia may be associated with cognitive fragmentation and thought disorder.

Even loud noises are partially gated out when they are immediately (~ 100 ms) preceded by a brief tone, or prepulse. This response inhibition by a prepulse is called 'prepulse inhibition' (PPI). It is not learned but is observed on the first trial (Hoffman, 1997); it is observed across many animal species, including amphibians (Yerkes, 1905) (cited in Hoffman, 1997) and it does not require attention, although it can be affected by attention (Dawson et al., 1997; Hackley and Boelhauwer, 1997). A recent study (Filion et al., 1998) (reviewed in Dawson et al., 1997) found that subjects who demonstrate greater PPI suffer less interference from the startling noise than subjects demonstrating smaller amounts of PPI. Consistent with this is a report (Karper et al., 1996) that less distractible psychotic patients have greater PPI.

PPI is reduced in patients with schizophrenia, and this reduction appears to be related to thought disorder (Perry and Braff, 1994). Animal studies of startle blink have shown that dopamine receptor D2 agonists, like apomorphine, cause reduced PPI, mimicking the PPI failure in schizophrenia, while D2 receptor antagonists reverse that effect (Mansbach et al., 1988). However, in studies of schizophrenics who take D2 receptor antagonists (eg., haloperidol), PPI failure is still present. Recent evidence suggests that clozapine restores apomorphine-disrupted PPI in rats (Swerdlow et al., 1997).

A prepulse preceding a startling stimulus by about 2 s or more facilitates the response to the noise. This is called 'prepulse facilitation' (PPF) and possibly reflects alerting, attention, or strategic processes (Graham, 1975), or voluntary selective attention, or automatically elicited generalized orienting (Hackley and Graham, 1991). Thus, with a short lead interval, pre-attentive inhibitory processes function to protect the initial processing of the prepulse; with longer intervals, strategic directing of attention or automatic orienting could occur. Importantly, the addition of sustained attentional tasks can affect both PPF and PPI (for

review, see Dawson et al., 1997). Blinks were affected similarly in controls and schizophrenics with a 2-s lead interval (Braff et al., 1978); they were facilitated, but not significantly.

Typically, only reflex blinks have been measured in startle modification paradigms. However, two developments have motivated examination of scalp recorded event-related brain potentials (ERPs) in conjunction with startle blink. First, parallels have been observed between failures in startle modification and suppression of P50 (Adler et al., 1985). However, it is unlikely that P50 suppression and PPI reflect similar mechanisms as they are uncorrelated in normal control subjects (Schwarzkopf et al., 1993). Second, techniques are now available to remove the overlapping effects of blinks and eye movements from scalp recorded ERPs (Brunia et al., 1989; Gratton et al., 1983; Miller et al., 1988) and to remove components of the ERP to the prepulse from the ERP to pulse (noise) (Simons and Perlstein, 1997; Woldorff, 1993). Studies of ERPs during PPI experiments have shown N1 and P2 inhibition in healthy young adults at short lead intervals (Perlstein et al., 1993), and P300 inhibited at short lead intervals in 9-year-old boys (Sugawara et al., 1994). No investigator has yet reported PPI effects on all three ERP components.

The circuit generating startle blink is quite well documented (Davis et al., 1982) and, in its simplest form, involves hindbrain structures of ventral cochlear nucleus, ventral nucleus of the lateral lemniscus, and the nucleus reticularis pontis caudalis. The circuit modifying startle blink inhibition with a prepulse has also been described (Swerdlow et al., 1995). In brief, the prepulse activates neural structures in the limbic system and basal ganglia, which work together to have a top-down influence on the response to the noise, inhibiting the reflex to the noise. Disruptions in medial prefrontal cortex and ventral hippocampus have been implicated in PPI failures in rats (Swerdlow et al., 1995). The circuit involved in PPF may include the amygdala when fear potentiates startle (Davis et al., 1993).

The circuts generating the different ERP components are not as well documented, and knowledge of them is based on studies using neurological patients (Knight et al., 1989), structural brain

imaging (Ford et al., 1994), functioning brain imaging (Menon et al., 1997), and magnetoencephalography and electrophysiology (Pantev et al., 1995; Reite et al., 1994; Reite et al., 1997). Although N1, P2 and P300 may depend on both sensory and non-sensory subcortical structures for their elicitation, their voltage on the scalp surface is mostly a reflection of cortical activity (Lutzenberger et al., 1987). The cortical generators of the N1 component of the ERP to a noise are probably widespread, involving diffuse polysensory cortical systems (Näätänen and Picton, 1987). Using magnetoencephalography, N1 generators have been located to the superior plane of the temporal lobe (Reite et al., 1994; Siedenberg et al., 1996; Tarkka et al., 1995). The P2 component often accompanies N1, but is dissociable from it experimentally (Oades et al., 1997; Roth et al., 1976), developmentally (Oades et al., 1997) and topographically (Roth et al., 1976). Nevertheless, based on magnetoencephalography, its generator appears close to that of N1 (Siedenberg et al., 1996; Tarkka et al., 1995). The generators of the P300 component to a target tone probably include the temporal–parietal junction (Menon et al., 1997), while to a non-target intrusive noise, its generators include more frontal structures (Ford et al., 1994). The circuits modifying the N1, P2 and P300 cortical responses are not known and might involve some elements of reflex blink modification circuits, but must involve other elements as well, since they emanate from different structures from startle blink.

By recording ERPs in a PPI paradigm in patients with schizophrenia, we have attempted to bring cortical evidence to bear on this gating failure in schizophrenics. In this investigation, we used three different lead intervals, 120, 500 and 4000 msec. The 120-ms lead interval was chosen as the most effective for eliciting PPI, through automatic, pre-attentive mechanisms. The 4000-ms lead interval was chosen to investigate facilitation, perhaps due to selective attention or automatic orienting (Graham, 1975). The 500-ms lead interval, typically used in P50 sensory gating paradigms, was used to facilitate comparison of blink suppression in this study to that reported in the literature.

Modification of N1, P2, and P300 with prepulses will reflect modification of sensory and cognitive resource allocation, occurring automatically at short lead intervals, and both automatically and strategically at long lead intervals.

2. Methods

2.1. Participants

Written informed consent was obtained from all subjects, and their guardians for those legally conserved. Exclusion criteria included history of significant head injury (loss of consciousness ≥ 30 min or neurological sequelae), current diagnosis of epilepsy, history of drug or alcohol dependence, or history of psychosurgery.

Patients were 15 men (42.2 years old, range 23–59) with a DSM-IV diagnosis of schizophrenia determined by the consensus of a research psychiatrist who conducted a semi-structured interview and a research assistant who employed the SCID (Structured Clinical Interview for DSM-III-R (Spitzer et al., 1989). All were in- or out-patients at the Department of Veterans Affairs Health Palo Alto Care System. Within 2 days of ERP testing, patients were clinically rated by two calibrated raters using the Brief Psychiatric Rating Scale (BPRS). As a group, their symptoms were only moderately severe (total BPRS = 35.3, range 20–44.5). All patients had been stable on medication for at least two weeks at the time of testing, 10 on atypical antipsychotics (clozapine, risperidone, olanzapine) and five on typical antipsychotics.

Controls were 20 men (43.5 years, range 28–54) recruited and screened by telephone interview and questionnaire to exclude those with a history of significant psychiatric or neurological disease, recent use of psychoactive drugs or other drugs with significant central nervous system effects, or alcohol consumption exceeding 50 g/day for a month or more. Having passed the telephone screen, they were invited into the laboratory and evaluated with the SCID for the presence of past

or current psychiatric diagnosis. Only those with no psychiatric diagnosis were included.

2.2. Testing

2.2.1. Startle modification paradigm

Subjects wore earphones and sat upright in an easy chair in a sound attenuated room. Subjects were presented with 10 of each of the six trial types shown in Fig. 1, noise alone (50 ms broadband, 115 dB sound pressure level, SPL), tone alone (25 ms, 1000 Hz, 85 dB SPL), continuous tone alone (4000 ms, 1000 Hz, 85 dB SPL), tone/noise pair with 120-ms lead interval (PP120) tone/noise pair with 500-ms lead interval (PP500), continuous tone/noise pair (4000-ms lead interval) (PP4000). Between 12 and 18 s elapsed between trials. Subjects were given verbal instructions to simply 'relax and listen'. The ambient noise in the recording chamber was approx. 40 dB SPL.

2.2.2. Auditory oddball paradigm

In the same environment used for the startle modification paradigm, subjects were presented with a series of 320 background tones (500 Hz, 70 dB SPL, 50-ms duration) and 80 target tones (1000 Hz, 70 dB SPL, 50-ms duration). Subjects were asked to press a reaction time (RT) button to the target tones, giving equal importance to speed and accuracy.

2.3. EEG and EOG

2.3.1. Record

Electroencephalogram (EEG) was recorded from the eight standard 10–20 scalp sites, Fz, Cz, Pz, Oz, T3, T4, C3, C4 with linked mastoid reference. Vertical electro-oculogram (EOG) was recorded from electrodes placed above and below the right eye, and horizontal EOG from electrodes placed at the outer canthus of each eye. EEG and
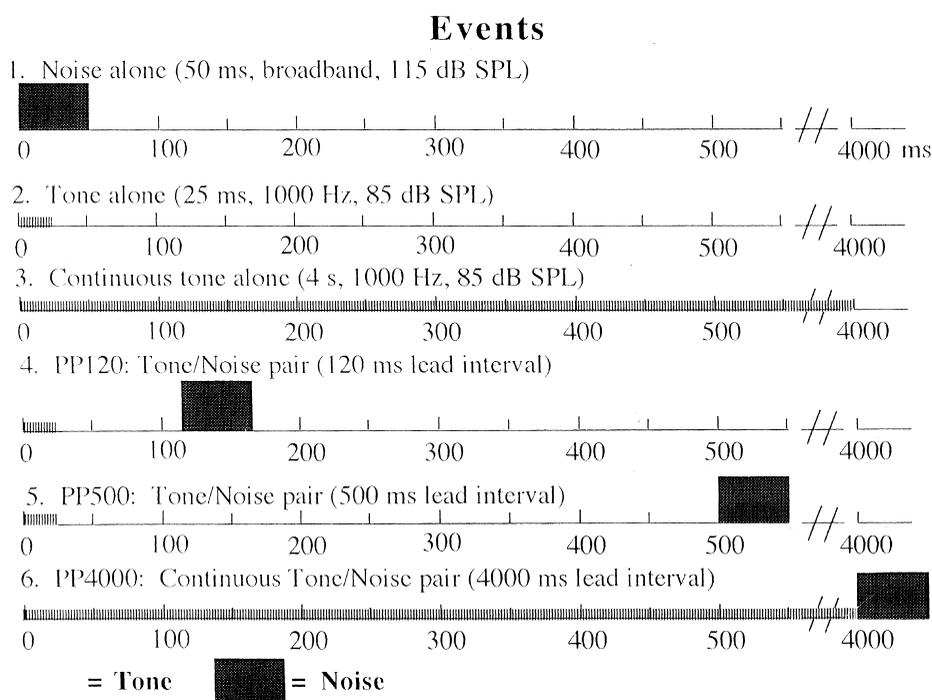

Fig. 1. Schematic of paradigm shows six event types: noise alone, tone alone, 4 s continuous tone alone, noise preceded 120 ms by the tone (PP500), and noise preceded by the continuous tone (PP4000). These event types occurred in a pseudo-random sequence, with 14–18 s inter-event intervals.

EOG were sampled every 5 ms for 1250 ms beginning 100 ms before stimulus onset. Band pass was 0.01–30 Hz. A Neuroscan STIM and SCAN system was used for stimulus presentation and data acquisition.

2.3.2. ERP data screening

Single trials were individually screened by computer algorithm before being included in the signal averages. For the auditory oddball paradigm, trials on which button press errors occurred were excluded from analysis. For both paradigms, single trials at each electrode were individually corrected for the effects of eye blinks and eye movements (Gratton et al., 1983; Miller et al., 1988). This method has been chosen by others (Perlstein et al., 1993) to study reflex blinks and ERPs, and its validity is equal to that of its alternatives (Brunia et al., 1989).[1]

2.3.3. Overlapping components

To minimize the contribution of potentially overlapping components from prepulses in response to noises (particularly relevant for the PP120 pairing), we subtracted the ERP elicited by tone alone from ERP to noise, appropriately adjusted in time, as has been done by others (Simons and Perlstein, 1997). A similar correction was also performed to minimize overlap from offset of continuous tone to its paired noise. It should be noted that this approach is only as good as the validity of its underlying assumptions, i.e. equivalence and additivity of responses elicited by prepulse alone and prepulse preceding the noise. Differences due to attentional effects and number of trials were minimized by having all events equiprobable.

2.3.4. ERP component identification and assessment

Responses were measured to the noise alone and in PP120, PP500, and PP4000 pairings. Responses to short and long tones presented alone were used in the subtraction procedure described above. N1 was measured as the most negative point between 50 and 150 ms. The startlingly loud noise elicits a parietally maximal component (Putnam and Roth, 1990) which in some subjects represents the merging of the P2 and P300, as can be seen in Fig. 2. Nevertheless, we assessed P2 and P300 separately by identifying P2 as the most positive peak between N1 and 225 ms only at Fz and Z, and P300 as the most positive peak between 280 and 600 ms at all sites. P50 was not measured because 10 trials in this paradigm were inadequate for overcoming this component's small signal-to-noise ratio. For the auditory oddball paradigm, N1 between 50 and 150 ms, P2 between N1 and 225 ms, and P300 between 280 and 600 ms were measured in the ERP to the target and background tones. Latencies of each component were measured at the peak of the component.

2.3.5. Startle blink measurement

Startle blink was measured from VEOG[2] tracings in two ways, from averages and from single trials. For the values based on averages, the 10 trials of each type were averaged together and the peak amplitude was measured relative to a pre-blink baseline, analogous to the method for measuring ERP peak values. For the values based on single trials, each blink was measured individually, again relative to a pre-blink baseline, and these values were averaged together. Thes two methods yielded almost identical patterns of results. Because of their similarity to ERP methods, values from the average VEOG tracing are reported below. Blink latencies were measured as the latency of the average peak amplitude of the blink, as well as the latency of the single trial peak amplitude, using a search window of 50–150 ms.

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[1]For removing the effects of startle blink from EEG, Perlstein et al. (1993) chose the Gratton et al. (1983) method for removing startle blinks from their EEG data because correction factors are computed on the ERP activity after the stimulus-synchronized activity has been removed. This is especially important in removing startle blink, rather than spontaneous blink, activity from EEG because it will reduce the estimate of the degree of correlation between stimulus-related blink (e.g. startle) and EEG activity. We have chosen to use the same algorithm.

[2]Although it is more traditional to measure blink amplitude from orbicularis oculi electromyogram (EMG) than VEOG, when both are used, they yield highly similar results (Putnam and Roth, 1990; Sugawara et al., 1994).
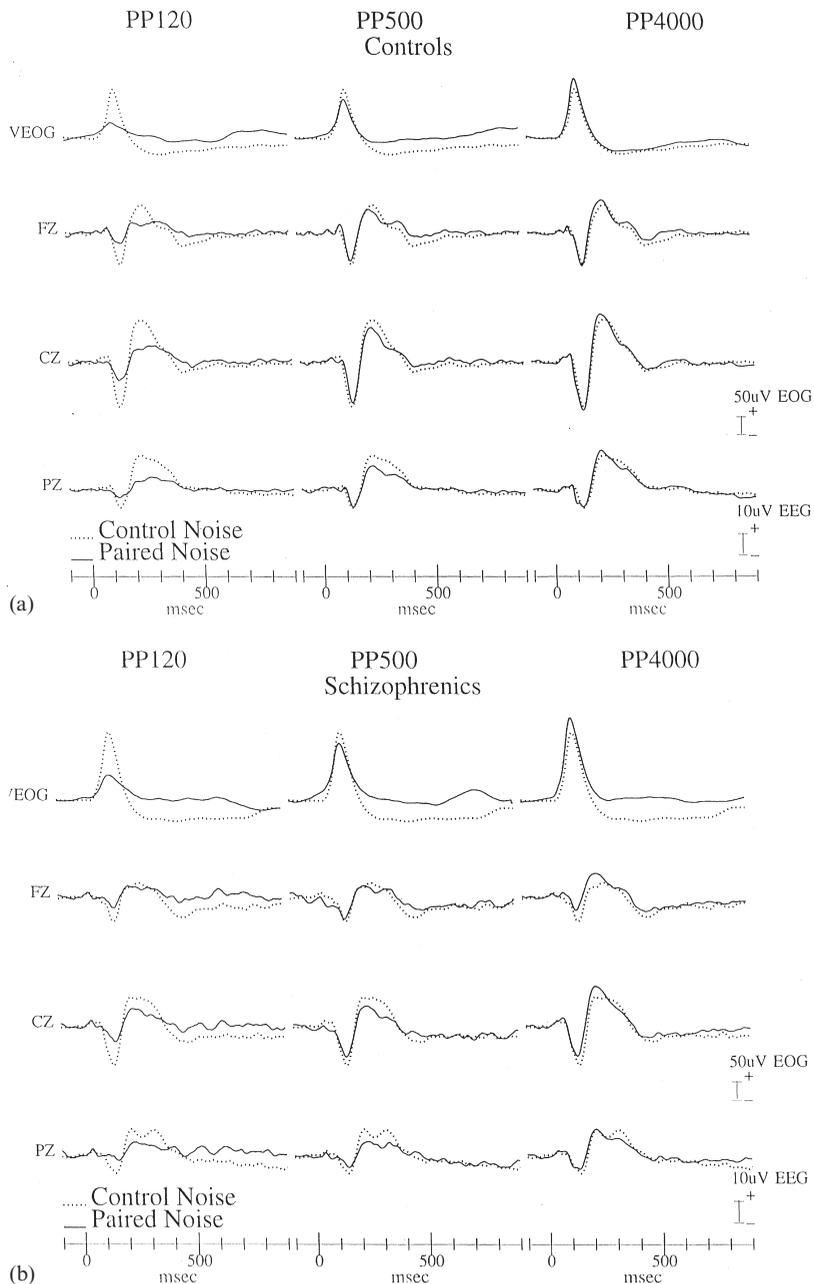
Fig. 2. (a) Grand average waveforms are shown for responses of controls to noises when presented alone (dotted line) or when preceded by a prepulse with a 120 ms (PP120), a 500 ms (PP500), or a 400 ms (PP4000) lead interval. The prepulse of PP120 and PP500 was a 25 ms tone. For PP4000 it was a 400 ms continuous tone. Blinks seen in the VEOG tracing have been mathematically removed from recordings for frontal (Fz), central (Cz) and parietal (Pz) sites. Positivity is plotted up. Data for one control subject, recorded at a faster sampling rate, are not included in the plot but were included in the anlaysis. (b) Same as (a) for patient with schizophrenia. Data for two patients, recorded at a faster sampling rate, are not included in the plot but are included in the analysis.

2.4. Statistical analysis

2.4.1. Startle modification paradigm

Amplitudes and latencies of blink, N1, P2 and P300 to the noise, presented alone and with the three prepulse intervals, were statistically compared using an analysis of variance (ANOVA) for the unrepeated factor of Diagnosis (Schizophrenics, Controls), and the repeated factors of Prepulse condition (Noise alone, PP120, PP500, PP4000), and Scalp Site (N1: Fz, Cz, P2: Cz, P300: Fz, Cz, Pz, Oz, C3, C4, T3, T4). Greenhouse–Geisser (G–G) corrections were made for repeated observations. The main effects of the prepulse condition were followed-up with *t*-tests on the difference scores between Noise Alone and the different Prepulse conditions at Fz and Cz for N1, at Cz for P2, and where significant for P300. In addition, ERPs to the Noise Alone were compared across groups. When significant interactions emerged, subanalyses were performed separately for the different levels of an interacting factor.

2.4.2. Auditory oddball paradigm

Analysis was performed as above for amplitude and latency of N1, P2, and P300 for the unrepeated factor of Group (Schizophrenics, Controls) and the repeated factors of Scalp Site (as above), and Event Type (Target/Background).

3. Results

3.1. Response modification paradigm

3.1.1. Startle blink

VEOG tracings of startle blink appear in Fig. 2 and plots of the mean values appear in Fig. 3. Blinks peaked at approx. 120 ms and their latency was not affected by the Prepulse condition. As expected, the Prepulse condition significantly affected the startle blink amplitude ($F(3,99) = 20.20$, G–G $p < 0.0001$). Startle blink was reduced with PP120 ($p < 0.0001$) and tended to be reduced with PP500 ($p < 0.06$), but was not facilitated with
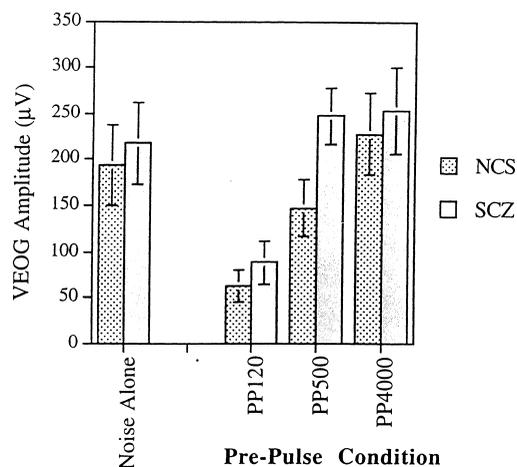

Fig. 3. Bar graphs showing VEOG amplitude to the Noise Alone and to the Noise preceded by different prepulses (PP120, PP500, and PP4000 ms) for normal controls and patients with schizophrenia.

PP4000 ($p = 0.125$).[3] Unexpected was the lack of interaction between Diagnosis and Prepulse condition ($F(3,99) = 0.01$, n.s.). Because previous findings were based on 120-ms lead intervals, we explicitly compared blinks with noise alone and PP120. Again, we failed to find an effect of Diagnosis ($t(33) = 0.0$, n.s.). For comparability with an earlier study (Braff et al., 1992), we excluded one patient and one control whose average blink for the first three noise alone trials was less than 100 µV; the Diagnosis × Prepulse condition interaction was still not significant ($t(31) = 0.03$, n.s.).

Single trial blink amplitudes were assessed across trials for each condition. While blink amplitude diminished differently across the ten trials of each Prepulse condition ($F(1,864) = 7.05$, G–G $p < 0.0001$), this effect was not affected by Diagnosis ($F(9,864) = 0.78$), n.s.), nor was there

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[3]It is important to note that in a group of young (18–25-year-old) controls (8 men, 4 women), we found both significant PPI at 120 ms ($p < 0.05$) and PPF with 4 s ($p < 0.005$). Differences in either age, educational attainment, or gender mix from the middle-aged male controls in this study might explain the discrepancy in PPF effects. In any case, our failure to find PPF in the controls is not due to paradigm or measurement differences between our study and those in the literature.

an interaction of Diagnosis $\times$ Prepulse condition $\times$ Trial (F(27,864) = 0.78, n.s.).

Blink latency was not affected by Diagnosis or Prepulse condition.

3.1.2. ERP components

N1 amplitudes are plotted in Fig. 4. N1 amplitude was affected by an interaction of Prepulse condition $\times$ Diagnosis (F(3,99) = 3.71, G–G $p < 0.05$) due to an effect of Diagnosis for PP4000 (t(33) = 3.06, $p < 0.005$) but not for the other conditions. Controls showed relative facilitation (an increase in N1 amplitude of 3.6 µV, $p < 0.08$, two-tailed), and the patients showed relative inhibition (a decrease in N1 amplitude of 5.0 µV, $p < 0.03$, two-tailed). There was also an effect of Prepulse condition (F(3,99) = 18.08, G–G $p < 0.0001$) and in particular, there was significant PPI for PP120 and PP500 in both groups. An interaction of Prepulse condition $\times$ Site (F(3,99) = 8.87, G–G $p < 0.006$) revealed that the effects were strongest at Fz and Cz. N1 amplitude to the Noise alone was not significantly reduced in the patients ($p = 0.18$). N1 latency was also affected by Prepulse condition ($p < 0.05$), being significantly shorter with PP120; this effect was not affected by Diagnosis.

P2 amplitude was affected by an interaction of Prepulse condition $\times$ Group (F(3,99) = 3.34, G–G $p < 0.04$), which was due to the more extreme reduction of P2 with PP120 in controls than in the patients (see Fig. 2 and Fig. 5), perhaps due to greater PPI in controls than in patients for PP120 (t(33) = 2.37, $p < 0.03$), with P2 being reduced from 28.3 to 11.0 µV in controls, but only from 21.8 to 13.8 µV in patients. Neither PPI with PP500 nor PPF with PP4000 were affected by Diagnosis. P2 to the Noise Alone was not significantly reduced in the patients ($p = 0.09$). The latency of P2 was not affected by Diagnosis or Prepulse condition.

For P300 amplitude there was a significant Prepulse condition $\times$ Site interaction (F(21,693) = 2.53, G–G $p \leq .05$), with the Prepulse condition effect being significant at Cz, Pz, and T3. At Pz, P300 to the noise alone was larger than to PP120 ($p < 0.0001$), PP550 ($p < 0.003$), and PP4000 ($p < 0.02$) (see Fig. 2 and Fig. 6). Similar effects were seen at Cz, except for PP4000 ($p \leq 0.10$). At T3, there was no evidence of PPI or PPF for any of the Prepulse conditions. Because of the specific interest in the effect of Diagnosis on PPI for PP120, the effects of Diagnosis in this condition for P300 at Pz were assessed. Significant PPI was found in both groups, as well as a trend for more reduction in the controls than in the patients
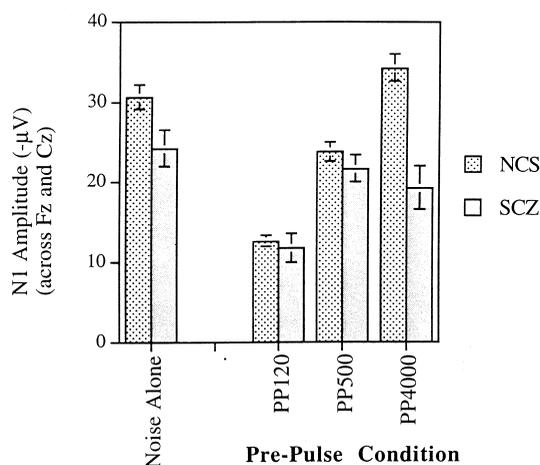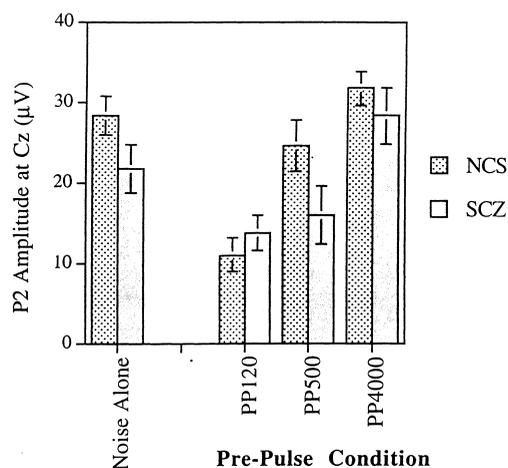

Fig. 4. Bar graphs showing mean N1 amplitude for Fz and Cz to the Noise Alone and to the Noise preceded by different prepulses (PP120, PP500, and PP4000 ms) for normal controls and patients with schizophrenia. The x-axis is inverted to enable comparison with the positive voltages of VEOG, P2, and P300.

Fig. 5. Bar graphs showing P2 amplitude at Cz to the Noise Alone and to the Noise preceded by different prepulses (PP1210, PP500, and PP4000 msec) for normal controls and patients with schizophrenia.
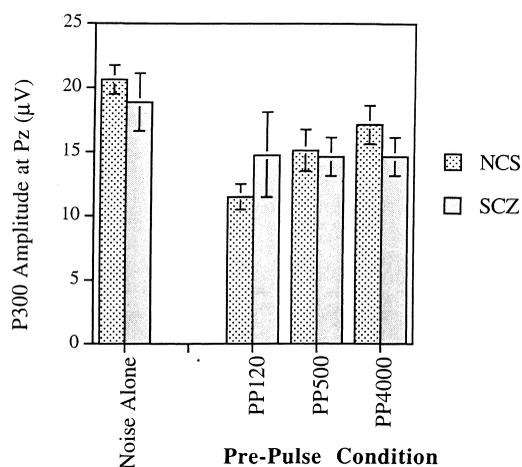
Fig. 6. Bar graphs showing P300 amplitude at Pz to the Noise Alone and to the Noise preceded by different prepulses (PP120, PP500, and PP4000 msec) for normal controls and patients with schizophrenia.

($p < 0.15$). PPI for PP500 was not affected by Diagnosis. P300 at Pz to the Noise Alone was not reduced in the patients ($p < 0.46$).

P300 latency was affected by Prepulse condition ($F(3,21) = 17.89$, G–G $p < 0.0001$) being latest with PP120 and earliest with PP4000 and noise alone. It was also affected by Site ($F(7,231) = 10.49$, G–G $p < 0.0001$), being earlier at the central sites than at T3, T4, and Oz.

3.2. Auditory oddball paradigm

3.2.1. ERP components

As can be seen in Fig. 7 and Fig. 8, N1 was smaller ($F(1,33) = 4.12$, $p = 0.05$) and later ($F(1,33) = 6,47$, $p < 0.02$) in patients than controls, and it was smaller to background than target events ($F(1,33) = 10.49$, $p < 0.003$); there were no significant interactions for amplitude or latency. P2 amplitude to the targets was not affected by Diagnosis, but was later in the patients than in the controls ($p < 0.04$). The P300 to targets was significantly smaller in patients than controls ($F(1,33) = 34.172$, $p < 0.0001$), suggesting that these patients are electrophysiologically representative of schizophrenics (Ford et al., 1992). Although there was a Diagnosis × Site interaction $F(6,198) = 6.034$, $p < 0.0001$), the effect of group

was significant at each site, but smaller at the lateral sites, P300 was not significantly later in the patients than controls ($p < 20$).

3.3. Summary of results

In summary, amplitudes of blinks, N1, P2 and P300 elicited by the startling noise without prepulses was not affected by schizophrenia; however, schizophrenia did affect how these measures responded to prepulses. With PP120, P2 was more inhibited in controls than patients, while N1, P300 and blinks were reduced equally in both groups. With PP500, there were no differences between groups for blinks or any of the ERP components. With PP4000, N1 was more facilitated in controls than in patients, while P2, P300 and blinks were equally unaffected in the two groups. Latency effects did not differ between groups: N1 and P300, but not P2, were affected by the prepulse condition with N1 being accelerated and P300 being slowed with PP120. In a traditional oddball paradigm, N1 and P300 were significantly reduced in this group of schizophrenics.

4. Discussion

Schizophrenia did not affect responses to startling noises alone, but did affect how prepulses modified responses to those noises. With N1, patients showed normal inhibition but lacked facilitation, and with P2, patients showed abnormal inhibition, but showed normal facilitation. With reflex blink and P300, inhibition was seen in both groups, but no facilitation. This pattern of results suggests that different neural circuits are involved in the blink, N1, P2 and P300 reflections of startle modification, and that they are differentially affected by schizophrenia.

Both attentional (Hansen and Hillyard, 1983) and sensory (Picton et al., 1974) factors should be considered as explanations for the N1 effects. N1 is larger with increases in attention, whether automatically drawn or strategically directed. Thus, enhancement of N1 in controls with PP4000 might suggest that attention was oriented toward the noise, and lack of enhancement in the patients

Auditory Oddball
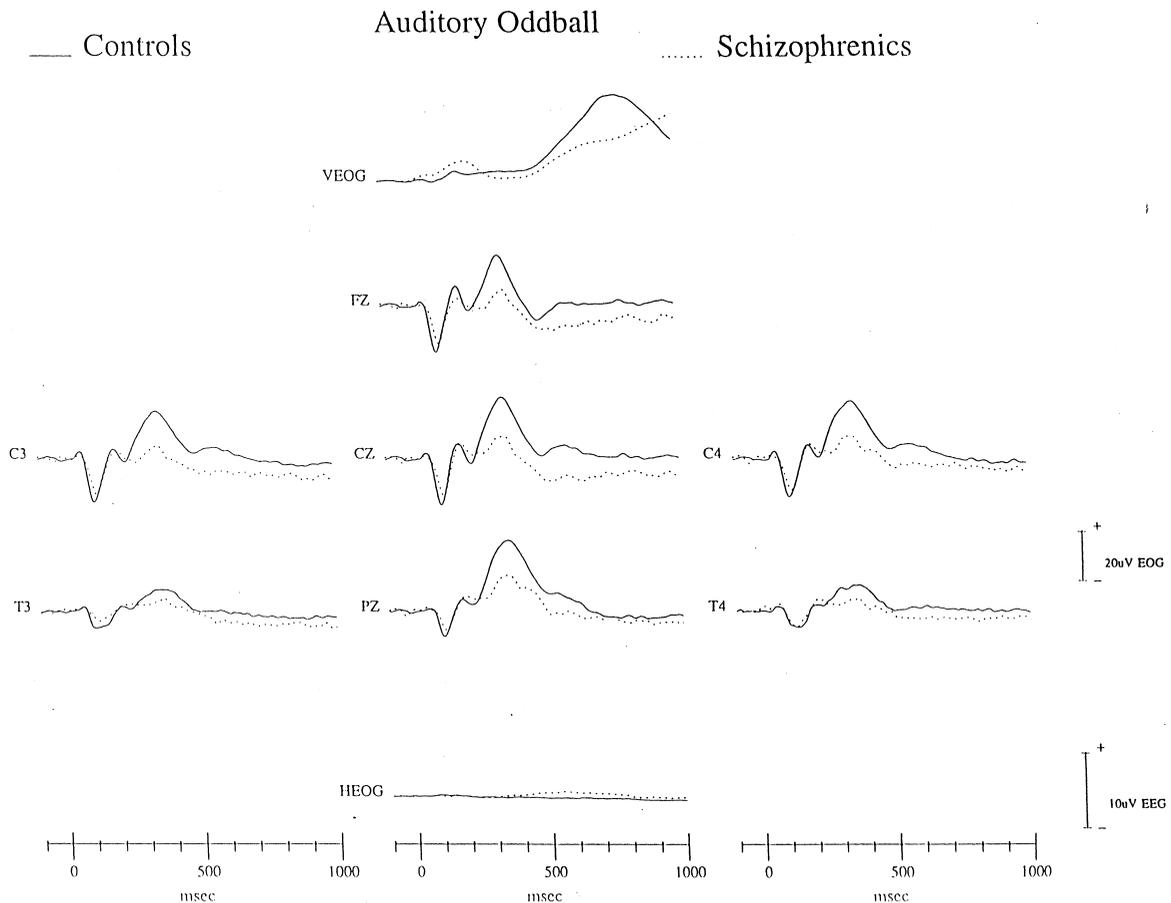
___ Controls   .... Schizophrenics

Fig. 7. Grand average waveforms are shown for responses of controls and schizophrenics to the auditory oddball tone. Blinks seen in the VEOG tracing have been mathematically removed from the recordings from scalp sites. Positivity is plotted up.

might suggest that attention was drawn away from the noise. This might reflect a difference in how the two groups respond to the 50% chance that the noise will follow the 4-s tone. Although conscious expectancy cannot be assumed during the 4-s tone, the interval is certainly long enough for it to occur. By the same logic, reduction of N2 with the short interval prepulse condition seen in both groups, might suggest that attention to the noise was directed away from the noise, possibly toward the prepulse itself. Because of the very short time interval involved, automatic influences are more likely than strategic. Thus, according to an attentional explanation, the N1 amplitude data would suggest that although attention was inhibited automatically in the patients, they did not

deploy it strategically, as did the controls. Because we did not intentionally manipulate cognitive variables such as attention or expectation, these interpretations are very speculative. However, we tentatively suggest that patients with schizophrenia have normal automatic but abnormal strategic deployment of attentional resources, as reflected in N1 amplitude.

Sensory factors provide less plausible explanations for the N1 effects. Intense and infrequent sounds elicit larger N1s (Picton et al., 1974) with stimulus qualities also affecting N1 amplitude in schizohprenia. Thus, smaller group differences in N1 are observed when stimuli are softer and occur with shorter interstimulus intervals (ISIs). However, in this study, noises were all equally
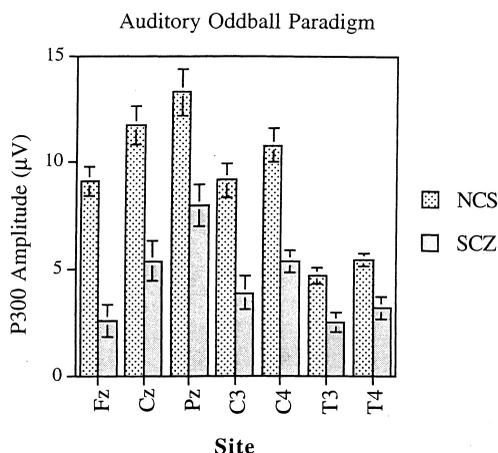
Fig. 8. Bar graph showing P300 amplitude from all sites recorded during the auditory oddball paradigm from normal controls and patients with schizophrenia.

intense, and the group difference was observed in N1 at PP4000 when no time elapsed between tone offset and the noise, i.e. a very short ISI.

In this study, patients show normal facilitation but abnormal inhibition of P2. P2 is often grouped with N1, and they are often measured together as a biphasic component, N1–P2; however, they are distinguishable along a number of dimensions. Topographically, P2 is centrally maximal and N1 is fronto-centrally maximal; P2 is later to develop in childhood than N1 (Oades et al., 1997); N1 and P2 are different in different subtypes of schizophrenia (Boutros et al., 1997). Therefore, it is not surprising that N1 and P2 were affected by prepulse conditions differently in controls and schizophrenics.

The effects of different Prepulse conditions on P300 form a third set of findings. P300 amplitude is reduced with PP120 similarly in both groups. This report of P300 amplitude modification by prepulses is the first for adult men but echoes a similar finding in young boys (Sugawara et al., 1994). P300 reduction with PP120 suggests that both groups allocated fewer resources to processing the noise when it was preceded by a prepulse. The lack of P300 enhancement with PP4000 suggests that attentional resources were not facilitated by this prepulse condition.

It is noteworthy that there were no group differ-

ences in the latencies of the components in this prepulse paradigm. In general, ERP amplitudes reflect the amount of a particular process, and ERP latencies reflect the speed of that process. Thus, our results suggest that groups do not differ in the speed of the processes but in the amount of resources or attention drawn or allocated to processing the stimuli.

That blinks, N1, P2, and P300 reflect dissociable processes has already been amply demonstrated in other studies. For example, N1 and P2 can be elicited without a P300 (Ford et al., 1976), P300 can be elicited without an N1 and P2 (Ford et al., 1976; Michalewski et al., 1982) and P300 and blink are dissociable (Putnam and Roth, 1990; Schupp et al., 1997). The neural circuits responsible for modifying N1, P2, and P300 must be independent and can occur in parallel.

A top-down circuit for startle modification has been proposed, based on both animal work and human neurological studies (Swerdlow et al., 1995). In this circuit the prepulse activates both the basal ganglia and the limbic system, and then this information feeds down to affect the bottom-up processing of the noise. The pre-frontal cortex may also be involved in response modification with prepulses because attention has a role in modulating the effects of prepulse condition on startle. Applying this model to the ERP components requires some knowledge of their neural generators and the structures supporting their generation. A review of the N1 and P2 literature (McCarley et al., 1991) suggested that while both N1 and P2 depend on the neocortex of the temporal lobe, N1 may be modulated by frontal activity (Knight et al., 1981), and P2 by inferior parietal lobe activity (Knight et al., 1989). However, McCarley et al. have also suggested that frontal lobe modulation of sensory activity may only be effective during active attention conditions. There are likely to be different generators for P300 elicited by startling noises and P300 elicited by auditory oddball targets (Ford et al., 1994). The P300 elicited by startling noises has not been studied with hemodynamic brain imaging, or with lesion studies. The novelty P300, however, has been associated with the frontal lobe, being reduced in patients with frontal lobe lesions (Knight, 1984).

Several independently operating top-down circuits need to be hypothesized separately to affect the generation of startle blink, N1, P2 and P300. Because our knowledge of the ERP generators is incomplete, we cautiously propose the following: the frontal lobe influence on N1 is normal in schizophrenia when invoked automatically, but when expectancies and strategies can play a role at the longest lead interval, it is abnormal. The frontal and/or inferior parietal lobe influence on P2 is abnormal in schizophrenia when these structures are activated automatically, but normal when strategies are allowed. The circuits modifying the startle blink and P300 responses operate normally in these patients with these parameters. Importantly, the primary generators of N1, P2, and P300 are normal in this group of patients, as reflected in the lack of a group effect on these components elicited by the noise when presented alone.[4]

A well-controlled drug study in patients with schizophrenia could possibly illuminate which structures are critical to successful inhibition and facilitation of N1, P2, and P300. For example, clozapine has a high affinity for neurons in the pre-frontal cortex compared with haloperidol (for review, see Brunello et al., 1995). If the pre-frontal cortex is involved in facilitation of N1 responses with the long lead interval, then the lack of facilitation seen in our patients might be reserved when patients are switched from haloperidol to clozapine. Although our patients were not randomly assigned to medication and although we only have five patients on clozapine and five patients on typcial antipsychotics, it is interesting that the patients on clozapine showed some facilitation of N1 (an increase of 1.6 μV), while the patients on typical antipsychotics showed marked inhibition of N1 (a decrease of 13.4 μV).

Though we obtained the expected P300 reduction in patients with schizophrenia in the auditory oddball paradigm, we observed only a very weak

reduction of P300 in the schizophrenia patients to the noise presented alone in the PPI paradigm. This finding is consistent with an earlier study (Roth et al., 1991) in which ERPS were elicited by isolated tones and noises, not surrounded by background tones, and suggest that P300 is only reduced in schizophrenic patients when a comparator process is invoked (Ford et al., 1992). Since we have previously observed large reductions of P300 to startling noises in patients with schizophrenia (Pfefferbaum et al., 1989), differences in sound quality (tones vs noises) alone cannot account for lack of P300 reduction. Possibly the P300s elicited by isolated events and target tones surrounded by standard tones are qualitatively different from each other and cannot be compared.

Despite demonstrating ERP indices of PPI failure, the patients in this study did not demonstrate the well-documented finding of reflex blink modification in schizophrenia (see review, Braff and Geyer, 1990) observed in passive (Bolino et al., 1992; Braff, 1993; Braff et al., 1992; Grillon et al., 1992) and active attention conditions (Dawson et al., 1993), and which also correlates with severity of thought disorder (Perry and Braff, 1994). Perhaps this was because they were psychopharmacologically well-treated outpatients (Perry et al., 1997), though with a mean BPRS of 35, they were mildly symptomatic. Despite a lack of reflex blink evidence for PPI failure, there was ERP evidence (P2 component) for PPI abnormality. Perhaps reflex blink PPI is a state reflection of the disease, while cortical reflections of PPI failure are a persistent trait of the disease.

Procedural and study parameter differences, listed in Table 1, may explain discrepant findings for startle blink. Most important may be the difference in background noise levels. Demonstration of startle blink PPI failure in patients with schizophrenia may require a low intensity prepulse tone relative to background noise. For example, our ambient background noise was only 40 dB, making the prepulse tone more evident. Our study and another failing to find PPI failure in schizophrenics (Dawson et al., 1993) did not use the more intense background noise used by those investigators who have found PPI failure

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[4]In interpreting these data, it is important to consider the possible effects of our procedure that subtract out the effects of overlapping components, especially for the PP120 condition with P2 to the prepulse affecting the N1 measurements to the noise.

Table 1
Summary of parameters in three PPI studies

	Braff et al. (1992)	Dawson et al. (1993)	This study
Antipsychotic meds	Typical	Typical	Atypical and typical
Mean age (years)	32.4 (SEM = 1.3)	24.1 (SD = 4.2)	42.2 (SEM = 2.4)
Patient status	Inpatients	Recent onset, outpatients	Mostly outpatients
Mean BPRS	29	25	35
Subject screening	Excluded non-startlers	No non-startlers in sample	Results not changed by excluding non-startlers
Data screening	Excluded trials with spontaneous blinks	Did not exclude trials with spontaneous blinks	Did not exclude trials with spontaneous blinks
Blink assessment	EMG	EMG	VEOG
Stimulus parameters	Pulse − 116 dB noise	Pulse = 100 dB noise	Pulse = 116 dB noise
	Prepulse − 85 dB noise	Prepulse = 70 dB tone	Prepulse = 85 dB tone
	Background = 70 dB noise	Background < 50 dB noise	Background = 40 dB noise

PPI, prepulse inhibition; EMG, electromyogram; VEOG, vertical electo-oculogram.

(Braff et al., 1992; Cadenhead et al., 1993; Grillon et al., 1992).

These data suggest that while some of the cortical generators of responses to startling noises are normal in patients with schizophrenia, the circuits involved in modifying their activity are abnormal. Recently, Andreasen et al. (1998) described three phases that schizophrenia research has passed through in the past few decades. The first is devoted to demonstrating that schizophrenia is a biological disease, the second is devoted to localizing specific symptoms with brain regions, and the third is devoted to understanding schizophrenia in terms of neural circuitry. The current findings of normal cortical responses but suggesting abnormal connections between cortical areas illustrate the third phase.

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