

Prepulse-Elicited Startle in Prepulse Inhibition

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Background: Prepulse inhibition (PPI) has become a major experimental paradigm in the study of psychiatric disorders. In this study, a potential confound in measurement and interpretation of PPI, namely startle reactions to so-called "nonstartling" prepulses, was examined.

Methods: Prepulses of 80, 85, and 90 dB(A) were presented on their own or followed by a pulse of 115 dB(A) (lead interval: 120 msec).

Results: Even at only 80 dB(A), prepulses presented alone elicited a response in about 50% of trials; and, except in the first stage of the experiment, responses became more frequent as prepulse intensity increased. Importantly, PPI at 80 and 85 dB(A) was negatively correlated with response probability to prepulses presented alone.

Conclusions: Prepulses reliably activate the very startle system that they are thought to inhibit, and a high level of responsiveness to prepulses is associated with relatively lower levels of PPI. These findings might hold important implications for clinical and psychopharmacologic studies of PPI, and we suggest that the extent and influence of prepulse-elicited startles should be routinely examined. *Biol Psychiatry* 2004;55:98–101 © 2004 Society of Biological Psychiatry

Key Words: Prepulse inhibition, acoustic startle reflex, habituation, sensorimotor gating, electromyography

A large number of experimental factors have been shown to modulate the acoustic startle reflex, the most important of which for psychopathologic research is weak prestimulation. If the startle stimulus (i.e., pulse) is preceded by a weak stimulus (i.e., prepulse), then the acoustic startle reflex is reliably reduced (Graham 1975), an effect referred to as prepulse inhibition (PPI).

Prepulse inhibition is considered one of the major experimental paradigms in the study of psychiatric disorders, especially schizophrenia (e.g., Braff et al 1978). The lower levels of PPI found in schizophrenic patients are thought to reflect an impairment in a sensorimotor gating process, by which "excess stimuli are screened or 'gated out' of awareness, so that an individual can focus attention on the most salient aspects of the stimulus-laden environment" (Braff et al 2001, p. 235). This paradigm has shown its value in studies of clinical status, psychopharmacology, and brain function. Often similar studies can be carried out in animals, allowing reasonably well-founded inferences to be made regarding underlying neural mechanisms. Thus, any potential confound in the measurement or interpretation of PPI would be of considerable significance.

The study presented here investigated just one such potential confound in PPI, namely, prepulse-elicited startle. Blumenthal (1999) pointed out that, at a sufficiently high intensity, prepulses might not just activate the inhibitory mechanism in the tegmentum but also activate the startle center in the pons. Depending on the method used, the startle threshold seems to vary between about 50 and 85 dB(A) (Berg 1973; Blumenthal 1988; Blumenthal and Goode 1991). A 70-dB(A) broadband noise stimulus with properties comparable to commonly used prepulses (rise time: .1 msec, duration: 20 msec) activates a startle response in about 60% of trials (Blumenthal and Goode 1991). Although most human PPI studies use prepulses of 84–87 dB(A) with durations of up to 40 msec (Braff et al 2001), prepulses continue to be regarded by many as "nonstartling" stimuli (e.g., Duncan et al 2001, p. 266).

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This might be justified because, in the above studies, stimuli were not presented against continuous background noise.

However, in the light of more conclusive evidence of prepulse-elicited startles in typical PPI paradigms, the claim that prepulses do not elicit the startle reflex, or a statement such as "the appropriate and standard practice in the literature is to use the term 'prepulse inhibition' only for conditions in which the prepulse does not elicit a startle response" (Braff et al 2001, p. 236), would seem problematic.

Recent unpublished evidence shows an association between prepulse reactivity and PPI (Yee et al, personal communication, 2003). Whole-body movement was measured in prepulse-alone trials in mice, and it was found that apomorphine and amphetamine, one a direct and the other an indirect dopamine agonist, attenuated PPI while enhancing reactivity in prepulse-alone trials. Antipsychotic drug treatment (haloperidol) was effective in antagonizing both the effects of apomorphine on PPI and on prepulse reactivity.

The possibility of prepulse-elicited startles might hold important implications for clinical and pharmacologic studies of PPI, but to date there have been, to our knowledge, no published reports examining prepulse-elicited startles and their association with PPI. Given the potential importance of this association, the aim of this article is to fill this gap in the literature by 1) determining the degree of prepulse-elicited startle responses in a typical PPI paradigm; and 2) examining the potential association of prepulse-elicited startle and PPI.

Methods and Materials

Participants

Eighty-one university students participated for course credits. Age ranged from 17 to 50 years (40 men, mean age = 22.35, SD = 5.53; 41 women, mean age = 22.88, SD = 5.92).

Stimuli

Four different stimuli were used, consisting of white noise presented over a background of 70-dB(A) white noise, via headphones: pulse (115 dB(A), 40 msec) and prepulses (20 msec) of three intensities (80, 85, and 90 dB(A)). All stimuli had a rise time of less than 1 msec. They were combined into seven different trial types: one pulse-alone trial, three prepulse-alone trials (80, 85, and 90 dB(A)), and three prepulse + pulse trials (80, 85, and 90 dB(A)). A lead interval (onset of prepulse to onset of pulse) of 120 msec was used. Trials were presented in a fixed pseudorandom order, separated by intertrial intervals of 9–23 sec

Table 1. Mean (SD) Pulse-Alone (115 dB(A)) Amplitude (Analog-to-Digital Units) across Blocks

	Mean	SD
Blocks 1–3	390.44	220.50
Blocks 4–7	314.30	195.77
Blocks 8–10	291.52	185.36

(mean = 15 sec) in 10 blocks, with each block containing one trial from each of seven trial types (i.e., 70 trials altogether).

Physiologic Data Collection

Equipment and scoring criteria have been described elsewhere (Corr et al 2002). Sound levels were measured and the equipment calibrated with a RadioShack Sound Level Meter (Cat. no. 33–2055) (RadioShack, Fort Worth, Texas). Electromyogram activity was recorded starting with the onset of the pulse in pulse-alone and prepulse + pulse trials and with the onset of the prepulse in prepulse-alone trials.

Design

A within-subjects design was used, with the factors prepulse intensity (three levels: 80, 85, and 90 dB(A)) and blocks (three levels: blocks 1–3, 4–7, and 8–10).

Data Scoring and Statistical Analysis

Prepulse inhibition (percentage reduction in amplitude [i.e., computed from only those trials in which a nonzero response was recorded; 3.25% of trials were rejected]) was calculated with this formula: $([\text{pulse-alone trial amplitude}] - [\text{prepulse} + \text{pulse trial amplitude}]/[\text{pulse-alone trial amplitude}]) \times 100$. To quantify responses to the prepulses presented alone, a measure of response probability was computed: the percentage of trials on which a response was recorded (i.e., number of nonzero response trials/total number of trials $\times 100$).

Procedure

Participants were asked to give their written informed consent and to complete a demographic questionnaire. Electromyogram recordings were taken in a moderately lit laboratory, with participants sitting in a reclining chair. Together with 3-min acclimation to the background noise and six pulse-alone acclimation trials, testing took approximately 23 min. After testing, participants were debriefed on the purpose of the experiment. The study was approved by the ethical procedures committee of the Department of Psychology, Goldsmiths College.

Results

One case had to be excluded because of equipment failure, one because of outliers, and one because it did not have at least one valid value out of the 10 trials for each type of pulse-alone or prepulse + pulse trial. Thus, the sample was reduced to 78 (40 men, 38 women). Reanalyzing the data with gender as an additional factor neither revealed any gender differences nor substantially changed any of the results reported below.

Prepulse Inhibition

Pulse-alone amplitude for different blocks is given in Table 1. Figure 1 illustrates that PPI 1) increased with rising prepulse intensity; and 2) habituated over time when prepulses of 80- or 85-dB(A) intensity were used.

Response Probability to Prepulses

Figure 2 illustrates that response probability to prepulses presented alone 1) increased with rising prepulse intensity in the

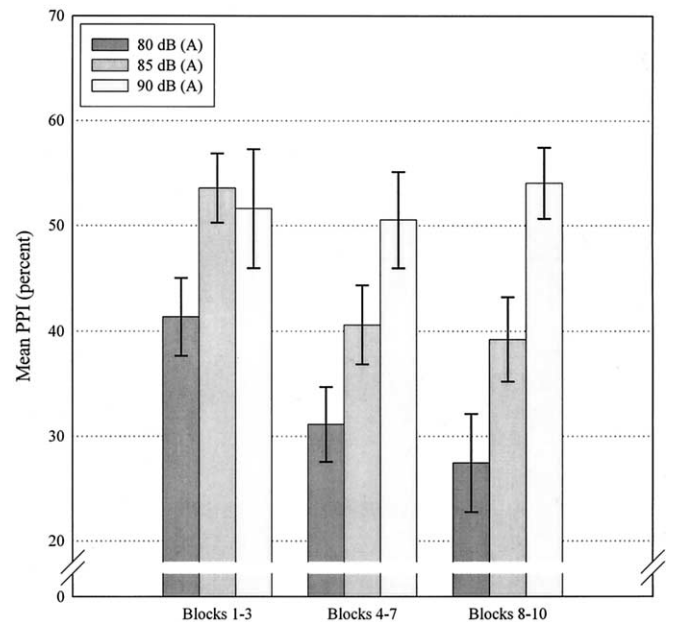


Figure 1. Mean percentage prepulse inhibition (PPI) separated by prepulse intensity and blocks. Error bars represent ± 1 SEM. A two-way (three prepulse intensity \times three blocks) multivariate analysis of variance (MANOVA) revealed a significant effect of prepulse intensity [$F(2,76) = 20.64, p < .001$; linear trend: $F(1,77) = 35.06, p < .001$], which indicates a linear increase in inhibition from 80 to 85 to 90 dB(A). A significant effect of blocks [$F(2,76) = 3.52, p < .05$; linear trend: $F(1,77) = 6.06, p < .05$] indicated that PPI habituated over time. The prepulse intensity \times blocks interaction also reached statistical significance [$F(4,74) = 2.54, p < .05$]. To uncover the nature of this interaction, one-way (three blocks) MANOVAs were carried out separately for each prepulse intensity. There was a significant effect of blocks at 80 dB(A) [$F(2,76) = 5.71, p < .01$; linear trend: $F(1,77) = 9.99, p < .01$] and at 85 dB(A) [$F(2,76) = 12.57, p < .001$; linear trend: $F(1,77) = 16.33, p < .001$] but not at 90 dB(A) [$F(2,76) = .32$], which indicates that PPI decreased from blocks 1–3 to 4–7 to 8–10 with 80- and 85-dB(A) prepulses but not with prepulses of 90 dB(A).

middle and later stages of the experiment; and 2) habituated over time.

Although prepulses reliably elicited startles, amplitudes were considerably smaller compared with pulse-alone amplitudes. For 85-dB(A) prepulses, for example, mean response amplitude ranged from 9.2 to 287.67 (mean: 35.21, SD: 38.1) analog-to-digital units.¹

¹In a follow-up experiment, the possibility that the responses scored in the prepulse-alone trials were an artifact of the scoring criteria we used was examined. Ten participants (seven men, three women) were presented with four types of trials: 85-dB(A) prepulse-alone trials, 115-dB(A) pulse-alone trials, prepulse + pulse trials (120-msec lead interval), and no-stimulus trials. "No-stimulus" means that the trial contained the usual response window without a stimulus being presented. Trials were presented in five blocks, with each block containing one from each of the four trial types, the total number of trials thus being 20. All other methodologic details were identical to the above experiment. Results concerning PPI and responsiveness to the prepulses were similar to those of the other experiment. Four responses occurred in a total of 50 no-stimulus trials. Thus, mean response probability for no-stimulus trials was 8% (SD = 13.98). This is comparable to results obtained by other studies (e.g., Graham and Murray 1977) and not significantly different from zero [$t(9) = 1.81$]. Therefore, it can be concluded that the responses scored in the prepulse-alone trials are not an artifact of the scoring criteria.

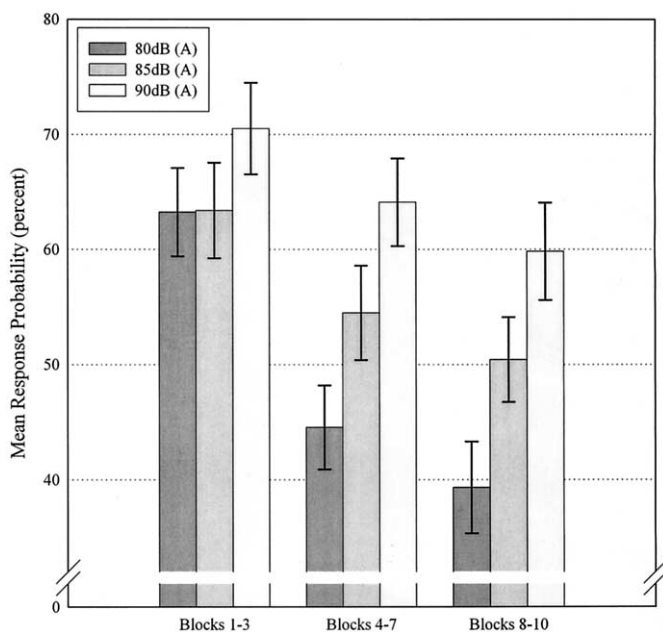


Figure 2. Mean response probability (percent) separated by prepulse intensity and blocks. Error bars represent ± 1 SEM. A two-way (three prepulse intensity \times three blocks) multivariate analysis of variance (MANOVA) revealed that response probability increased with prepulse intensity, rising from 80 to 85 to 90 dB(A) [$F(2,76) = 20.84, p < .001$; linear trend: $F(1,77) = 41.37, p < .001$]. Furthermore, there was a significant effect of blocks [$F(2,76) = 20.65, p < .001$]; responses to prepulses became less frequent from blocks 1–3 to 4–7 to 8–10 [linear trend: $F(1,77) = 34.26, p < .001$]. The prepulse intensity \times blocks interaction also reached statistical significance [$F(4,74) = 2.83, p < .05$]. Therefore one-way (three prepulse intensities) MANOVAs were conducted separately for blocks 1–3, 4–7, and 8–10. In blocks 1–3 there was no significant effect of prepulse intensity [$F(2,76) = 2.61$]; but significant effects of prepulse intensity and significant linear trends were found both in blocks 4–7 [$F(2,76) = 19.03, p < .001$; linear trend: $F(1,77) = 38.55, p < .001$] and blocks 8–10 [$F(2,76) = 10.83, p < .001$; linear trend: $F(1,77) = 21.77, p < .001$]. Thus, participants were more likely to respond to prepulses of higher intensities in the middle and last stages of the testing session but not at the beginning, where they responded to all prepulses equally frequently regardless of their intensity.

Correlations between PPI and Response Probability

Table 2 shows that, with respect to 80- and 85-dB(A) prepulses, high responsiveness to prepulses seems to be associated with lower levels of PPI.

Discussion

We examined the frequency of prepulse-elicited startle reactions at intensities typically used in PPI studies. Prepulse-elicited reactions were observed at the lower intensity of 80 dB(A). In the middle and later stages of the experiment, responses became more frequent as prepulse intensity increased from 80 to 85 to 90 dB(A); and startle reactions to the prepulses habituated over the testing session. In a follow-up study (see footnote), we eliminated the possibility that the observed prepulse-elicited startles were the result of spontaneous blinks, and a spurious artifact of the use of too liberal a response criterion. Thus, prepulses reliably activate the very response system they are thought to inhibit. The experiment also sheds light on the question of the association of prepulse-elicited startles and PPI. At prepulse intensity of 80 dB(A), and to a lesser extent 85 dB(A), PPI was negatively correlated with response probability to prepulses presented alone.

Table 2. Pearson Correlations between Percentage Prepulse Inhibition (PPI) at Three Prepulse Intensities, Pulse-Alone Amplitude (115 dB(A)), and Response Probability of Prepulse-Elicited Startles at Three Prepulse Intensities

	PPI 80 dB(A)	PPI 85 dB(A)	PPI 90 dB(A)	Pulse-Alone Amplitude
Pulse-Alone Amplitude	-.259 ^a	-.171	-.066	
Response Probability				
80 dB(A)	-.225 ^a	-.132	-.012	.173
85 dB(A)	-.296 ^a	-.217	-.077	.294 ^b
90 dB(A)	-.354 ^b	-.271 ^a	-.071	.408 ^b

PPI at 80 and 85 dB(A) prepulses is negatively correlated with response probability to prepulses presented alone (the correlation between PPI at 85 dB(A) and response probability to prepulses of 85 dB(A) is close to formal statistical significance [$p = .06$]). This seems to indicate that high responsiveness to prepulses is associated with lower levels of PPI.

^a $p < .05$, two-tailed.

^b $p < .01$, two-tailed.

It should be assumed that prepulse-elicited startles also occur in most clinical and pharmacologic studies, because the stimuli used here were chosen to be characteristic of a typical PPI paradigm; however, whether this finding has any other consequences than demanding a more cautious choice of words when discussing the role of “nonstartling” prepulses in PPI depends on whether a direct influence of prepulse-elicited startle on PPI can be demonstrated, and also on whether there is a difference in brain processes between inhibition caused by startle-eliciting prestimuli and inhibition caused by nonstartling prestimuli.

The present results, and the unpublished data from Yee et al (personal communication), which show that apomorphine (and amphetamine) enhances prepulse reactivity and attenuates PPI, whereas haloperidol antagonizes both these effects, suggest that prepulse-elicited startle is of theoretic importance. Results concerning the relationship of PPI and resting blink rate, a marker of dopamine function (Elsworth et al 1991; Lawrence and Redmond 1991) and a measure that might be related to frequency of prepulse-elicited blink reflexes, seem to support this assumption. Swerdlow et al (2002) showed that a lower level of PPI, which is also mediated by dopamine (e.g., Abduljawad et al 1998), is associated with increased resting blink rate.

It might be argued that recording responses to the prepulses in prepulse-alone trials is a weakness of the current experiment; however, there is no reason to believe that the results would have been any different if responses had been recorded in prepulse + pulse trials, because the occurrence of a to-be-measured event cannot be influenced by something that happens after this event. Still, it would be desirable to record responses to both prepulses and pulses within the same trial and compare prepulse + pulse trials on which prepulses did and did not elicit a startle.

Our first conclusion from this study is that prepulses are not “nonstartling.” Second, and most importantly, a high frequency of prepulse-elicited startles is associated with impaired PPI (we have since replicated these effects in two studies in our laboratory). Our data do not allow causal inferences to be drawn; however, close attention to the processes involved in PPI reveals a hidden complexity to the phenomenon, which is often defined as a simple operational measure of sensorimotor gating. The present data do not suggest that it is not; but they do counsel caution when interpreting clinical and pharmacologic results:

specifically, it will be important for future research to establish the extent to which PPI findings are a result of 1) sensorimotor gating, or 2) prepulse-elicited startles. At the very least, we propose that future PPI studies should take independent measures of prepulse-elicited startle reactions. A more satisfactory solution might be to develop prepulses that are not so prone to startle elicitation, such as ramped prepulses. Blink thresholds are significantly higher for stimuli with longer rise times (Berg 1973; Blumenthal and Goode 1991), whereas PPI does not seem to be affected by changes in prepulse rise time (Blumenthal and Levey 1989).

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- Abduljawad KA, Langley RW, Bradshaw CM, Szabadi E (1998): Effects of bromocriptine and haloperidol on prepulse inhibition of the acoustic startle response in man. *J Psychopharmacol* 12:239–245.
- Berg KM (1973): Elicitation of acoustic startle in the human. *Diss Abstr Int* 34:5217B–5218B.
- Blumenthal TD (1988): The startle response to acoustic stimuli near startle threshold: Effects of stimulus rise and fall time, duration, and intensity. *Psychophysiology* 25:607–611.
- Blumenthal TD (1999): Short lead interval startle modification. In: Dawson ME, Schell AM, Böhmelt AH, editors. *Startle Modification: Implications for Neuroscience, Cognitive Science, and Clinical Science*. Cambridge: University Press, 51–71.
- Blumenthal TD, Goode CT (1991): The startle eyeblink response to low intensity acoustic stimuli. *Psychophysiology* 28:296–306.
- Blumenthal TD, Levey BJ (1989): Prepulse rise time and startle reflex modification: Different effects for discrete and continuous prepulses. *Psychophysiology* 26:158–165.
- Braff DL, Geyer MA, Swerdlow NR (2001): Human studies of prepulse inhibition of startle: Normal subjects, patient groups, and pharmacological studies. *Psychopharmacology* 156:234–258.
- Braff DL, Stone C, Callaway E, Geyer M, Glick I, Bali L (1978): Prestimulus effects on human startle reflex in normals and schizophrenics. *Psychophysiology* 15:339–343.
- Corr PJ, Tynan A, Kumari V (2002): Personality correlates of prepulse inhibition of the startle reflex at three lead intervals. *J Psychophysiol* 16:82–91.
- Duncan E, Madonick S, Chakravorty S, Parwani A, Szilagyi S, Efferen T, et al (2001): Effects of smoking on acoustic startle and prepulse inhibition in humans. *Psychopharmacology* 156:266–272.
- Elsworth JD, Lawrence MS, Roth RH, Taylor JR, Mailman RB, Nichols DE, et al (1991): D1 and D2 dopamine receptors independently regulate spontaneous blink rate in the vervet monkey. *J Pharmacol Exp Ther* 259:595–600.
- Graham FK (1975): The more or less startling effects of weak prestimulation. *Psychophysiology* 12:238–248.
- Graham FK, Murray GM (1977): Discordant effects of weak prestimulation on magnitude and latency of the blink reflex. *Physiol Psychol* 5:108–114.
- Lawrence MS, Redmond DE Jr (1991): MPTP lesions and dopaminergic drugs alter eye blink rate in African green monkeys. *Pharmacol Biochem Behav* 38:869–874.
- Swerdlow NR, Wasserman LC, Talledo JA, Casas R, Bruins P, Stephany NL (2002): Prestimulus modification of the startle reflex: Relationship to personality and physiological markers of dopamine function. *Biol Psychol* 62:17–26.