Published in final edited form as:

Behav Neurosci. 2007 December ; 121(6): 1372–1382. doi:10.1037/0735-7044.121.6.1372.

Motivated Attention and Prepulse Inhibition of Startle in Rats: Using Conditioned Reinforcers as Prepulses

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Abstract

In humans, prepulse inhibition (PPI) of startle is greater during attended prestimuli than it is during ignored prestimuli, whereas in rats, most work has focused on passive PPI, which does not require attention. In the work described in this article, researchers developed a paradigm to assess attentional modification of PPI in rats using motivationally salient prepulses. Water-deprived rats were either conditioned to attend to a conditioned stimulus (CS; 1-s, 7-dB increase in white noise) paired with water (CS⁺ group), or they received uncorrelated presentations of white noise and water (CS⁰ group). After 10 conditioning sessions, startle probes (50 ms, 115 dB) were introduced, with the CS serving as a continuous prepulse. Three experiments examined PPI across a range of prepulse intensities (4–10 dB) and stimulus onset asynchronies (SOAs; 30–960 ms). PPI was consistently reduced in the CS⁺ group, particularly with a 10-dB prepulse and a 60-ms SOA. Thus, PPI in rats differed between attended and ignored prestimuli, but the effect was reversed in the results of research with humans. A fourth study eliminated the group difference by reversing the CS–water contingency. Methodological and motivational hypotheses regarding the current findings are discussed.

Keywords

attention; startle; prepulse inhibition; motivation; reinforcement

Prepulse inhibition (PPI) of startle has been extensively studied in both humans (Braff, Geyer, & Swerdlow, 2001; Graham, 1975) and rodents (Ison, 1978; Swerdlow, Geyer, & Braff, 2001). This effect is characterized by the attenuation of the startle response (eyeblick in humans, whole-body movement in rats) when the startle probe is preceded by a nonstartling stimulus, or prepulse, with a prepulse-to-probe stimulus onset asynchrony (SOA) between 50 and 500 ms (Blumenthal, 1999). PPI is thought to reflect a relatively automatic gating mechanism (Braff & Geyer, 1990) that may serve to protect the initial processing of stimuli (Graham, 1975). Although the probe and prepulse may be auditory, visual, or tactile, brief noise bursts or tones are the most common stimuli.

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Given the clear parallels in PPI in humans and rats (e.g., Swerdlow, Braff, Taaid, & Geyer, 1994) PPI has been utilized as a cross-species model in neurobiological and psychopharmacological research (Braff et al., 2001; Geyer, Krebs-Thomson, Braff, & Swerdlow, 2001; Swerdlow et al., 2001). Extending the gating-mechanism hypothesis, changes in PPI due to various drugs are often interpreted as changes in attentional processing. For example, low doses (0.001–0.01 mg/kg) of nicotine increased PPI in rats (Acri, Morse, Popke, & Grunberg, 1994), and acute subcutaneous nicotine increased PPI in human nonsmokers (Kumari, Cotter, Checkley, & Gray, 1997). Such effects are sometimes interpreted as reflecting nicotine's enhancement of attention. However, the use of the simple PPI paradigm as an index of attentional processing may be limited to relatively automatic gating or filtering and not active, effortful attentional processing. This is evident in findings that PPI is observed in the absence of conscious awareness of the prepulse (Postma, Kumari, Hines, & Gray, 2001) and during sleep (Silverstein, Graham, & Calloway, 1980) in humans, as well as in decorticate rats (Ison, O'Connor, Bowen, & Bocirnea, 1991).

A modified PPI paradigm allows the assessment of both controlled and automatic attentional processes in humans (Dawson, Hazlett, Filion, Nuechterlein, & Schell, 1993; Filion, Dawson, & Schell, 1993; Jennings, Schell, Filion, & Dawson, 1996; Schell, Wynn, Dawson, Sinaii, & Niebala, 2000). This attentional modification of PPI paradigm often involves a series of tone stimuli of two different pitches. Participants are paid to attend to tones of one pitch while ignoring tones of the other pitch, and the tones serve as continuous prepulses. The ignored tones cause PPI, but PPI during attended tones is typically enhanced at the 120-ms SOA, presumably reflecting voluntary shifting of attentional resources toward the processing of the prepulse stimulus (Thorne, Dawson, & Schell, 2005). By examining PPI during ignored and attended prepulses, both relatively automatic attentional gating and controlled attentional processing can be examined in one paradigm (see also Filion & Poje, 2003), providing a useful tool for assessing attention in basic and applied settings.

Indeed, initial work suggests that the tone-discrimination paradigm may be more sensitive to deficits in controlled attentional processing as well as to drug effects on attentional processes than is the passive PPI paradigm. For example, a number of studies have failed to observe diminished passive PPI among children with attention-deficit/hyperactivity disorder (ADHD; Castellanos et al., 1996; Ornitz, Hanna, & de Traversay, 1992). In a recent study, we compared PPI in the tone-discrimination paradigm among boys with and without ADHD, reasoning that deficits in controlled processing would not be evident in the passive paradigm (Hawk, Yartz, Pelham, & Lock, 2003). Boys with ADHD were tested twice, once after a low (0.3 mg/kg) dose of the stimulant methylphenidate and once following placebo administration. The two groups showed comparable PPI during ignored tones, and methylphenidate had no effect on PPI during ignored tones. However, in comparison with control participants, ADHD boys showed a lack of attentional modification of PPI (i.e., enhanced PPI during attended tones vs. ignored tones) at the 120-ms SOA in the placebo condition. This deficit was ameliorated during the active medication condition. Thus, the attentional modulation of the PPI paradigm appears to be a useful tool for assessing automatic gating and controlled attentional processes (Dawson, Schell, Swerdlow, & Filion, 1997) in addition to the drug effects on these processes.

Although these data are promising, it is difficult to integrate human work on the attentional modification paradigm with animal work that has focused almost exclusively on passive PPI. Beyond evidence that PPI in rats may habituate under some circumstances (Gewirtz & Davis, 1995), we are aware of only one published rat study that has attempted to manipulate active, controlled attention to prestimuli. In this recent work, Röske and Koch (2006) paired a tone conditioned stimulus (CS) with shock and subsequently provided training with a visual conditioned inhibitor, a light indicating that the tone CS would not be followed by shock. PPI was assessed before and after training. PPI during presentation of the conditioned inhibitor

increased after training (PPI to the tone CS did not change with training). The authors interpret the findings as initial evidence of attentional modification of PPI in rats.

Although these data are encouraging, Röska and Koch (2006) were quick to point out the limitations of their paradigm and findings. Most notably, because of difficulties in combining the temporal features of fear conditioning and PPI, only a 300-ms SOA was used in the research. This is much later than in the human work, in which attentional modification is typically evident at 120 ms and PPI SOAs beyond 240 ms are rarely considered. Moreover, most rat PPI studies also focus on earlier SOAs, typically in the range of 60 to 120 ms. Thus, this limitation is a potentially serious one for a paradigm designed to parallel the human literature and allow for cross-species comparisons.

The goal of the present series of studies, conducted before the publication of Röska and Koch's (2006) provocative work, was to develop a PPI paradigm in rats that allowed for the examination of controlled attention using appetitive prestimuli and more typical SOAs. In addition, we hoped such a paradigm might provide a possible parallel to attentional modification of PPI paradigms used with humans. Such cross-species paradigms would allow us to further our understanding of basic attentional processes, mental disorders (e.g., schizophrenia, ADHD), and related psychopharmacology.

Designing a paradigm to assess controlled attention in animals raises several issues. Chief among these is the question of how to operationally define "attended" and "ignored" prestimuli. Given limited attentional resources, it is theorized that an organism directs attention toward salient information in the environment, such as reward- and threat-related stimuli (e.g., Lang, Bradley, & Cuthbert, 1997). Whereas Röska and Koch (2006) focused on threat-related stimuli, we examined appetitive stimuli. The latter appears to more closely parallel existing human work. Indeed, a monetary incentive is usually offered for performance on the tone-discrimination task, and though incentives are not necessary to obtain attentional modification of PPI (e.g., Hazlett, Dawson, Schell, & Nuechterlein, 2001), the effect appears to be enhanced by the presence of incentives (Ashare, Hawk, & Mazzullo, in press; Hawk, Redford, & Baschnagel, 2002).

In our research, attention was manipulated between subjects via conditioning. Water-deprived rats were provided with water as a reinforcer during conditioning and the PPI assessment. Half of these water-deprived rats were conditioned to associate a white-noise prepulse with a water reward (CS⁺ group), whereas the other half were given water independent of the prepulse (CS⁰; Rescorla, 1967). From an attention standpoint, the biologically relevant CS⁺ should garner greater attention than should the motivationally neutral CS⁰. Therefore, we hypothesized that PPI would be greater for the CS⁺ (attend) group than in the CS⁰ (ignore) group.

However, we also recognized an opposing prediction based in the neurophysiology of appetitive motivation and of PPI. It has long been known that mesolimbic dopamine release accompanies the presentation of primary reinforcers and that dopamine plays an important role in appetitive motivation and reward-related learning (Kelley, 2004; Kelley & Berridge, 2002; Schultz, 2006). Relevant to the current conditioning paradigm, it has also been repeatedly demonstrated that as CSs are repeatedly paired with the presentation of such natural rewards, the CSs themselves come to elicit a dopamine response (e.g., Schultz, Dayan, & Montague, 1997). Therefore, we would predict that the CS⁺ in the present experiments would result in phasic release of mesolimbic dopamine. It is interesting to note that there is a large literature regarding dopamine and PPI. Dopamine agonists disrupt PPI in rats (Geyer et al., 2001; Mansbach, Geyer, & Braff, 1988) and humans (see Braff et al., 2001, though this effect is not as robust in humans; see Swerdlow, Eastvold, et al., 2002, and Swerdlow et al., 2003), and this

disruption can be reversed in rats by administration of dopamine antagonists (Geyer et al., 2001; Mansbach et al., 1988). Consequently, we also considered the hypothesis that the CS⁺ group would show diminished PPI, relative to the CS⁰ group.

Both prepulse intensity and SOA are important parameters in PPI studies, and some group differences and pharmacologic manipulations are evident only within certain prepulse parameters (Swerdlow, Stephany, et al., 2002). Therefore, the first experiment examined PPI in both groups at three different prepulse intensities (4, 7, and 10 dB above background) to determine whether group differences were more apparent at some intensities than others. An SOA of 120 ms was used in the first experiment, as this is when optimal attentional modification is usually observed in humans (Dawson et al., 1993; Filion et al., 1993). However, it is possible that the time course of attentional effects on PPI vary across species. Therefore, Experiments 2 and 3 examined a broader set of SOAs to better characterize the group differences found in Experiment 1.

Finally, to demonstrate that the group differences observed in Experiments 1–3 were due to conditioning and not to preexisting differences, Experiment 4 assessed the effects of reversing CS conditions between groups. Given the extensive training in this study, a full reversal of PPI was not expected; however, we predicted that the reversal of contingencies would disrupt or eliminate any previously observed group differences.

General Method

Experimental Subjects

A single sample of sixteen male Holtzman Sprague–Dawley rats (Harlan, Indianapolis, IN) was used in all experiments. The rats were housed in pairs and kept on a 12-hr light–dark cycle with lights on at 7:00 a.m. All rats had ad libitum access to food. The rats were on a restricted water protocol, with water accessible only during testing and for an additional 20-min period each day. This study was conducted in accordance to the guidelines set up by the Institutional Animal Care and Use Committee of the University at Buffalo.

Apparatus

Startle responding was assessed using two commercially available startle chambers (SR-LAB; San Diego Instruments, San Diego, CA). Each chamber contained a Plexiglas cylinder (10.2 cm in diameter) sitting on top of a 20.3 cm × 12.7 cm Plexiglas platform. Startle responses were measured as transduced cylinder movement via a piezoelectric sensor attached to the platform. Specifically, startle magnitude was defined as peak increase in voltage from 5 to 150 ms after startle probe onset, relative to baseline (0–5 ms after probe onset). We used the SR-LAB Calibration System to calibrate the sensitivity of the startle response system to within 1% variability between chambers.

Water was presented to the rats in a small Plexiglas bowl located at one end of the restraint tube via syringe pumps (PHN-100; MED Associates, St. Albans, VT), which pushed 60-ml syringes (Becton Dickinson, Franklin Lakes, NJ). The pumps delivered 50 µl of water each time they were activated. This amount of water is large enough to be highly motivating to water-restricted rats, yet small enough to avoid satiation during the course of an experimental session.

Stimuli and General Procedure Across Experiments

The CS or prepulse stimulus was a 1-s duration white noise presented 4, 7, or 10 dB above the controlled 62-dB background white noise provided in the startle chambers. Startle probes were 115-dB bursts of white noise lasting 50 ms in duration. All acoustic stimuli were presented by

SR-LAB via the chamber speaker. Acoustic stimuli were calibrated (dB–A scale) with a sound level meter (Model SA 155; Radio Shack, Fort Worth, TX) placed inside the testing cylinder.

Half of the rats were conditioned to associate the prepulse stimulus with the presentation of water (CS⁺ group). The other half received uncorrelated presentations of the prepulse and water (CS⁰ group; see *Conditioning* below).¹

Each trial consisted of a 1,000-ms baseline period, a 1,000-ms prepulse period, and a 1,000-ms postprepulse period. Trials were separated by a variable-length intertrial interval (ITI) that averaged 30 s in duration.

Each experimental session began with a 5-min acclimation period followed by 10 habituation startle probe trials. Following the habituation trials, 72 trials were presented in a pseudorandom order, with 24 prepulse-alone trials, 24 probe-alone trials, and 24 prepulse and probe trials.

Half of the subjects were tested in the data collection boxes on Monday and Wednesday, and the other half were tested on Tuesday and Thursday. On days when a subject was not in the data collection box, it was in the practice box where it was still presented with the prepulse and water. Subjects were not tested Friday through Sunday but remained on the water restriction protocol.

Data Analysis

For each experiment, percent prepulse modification was computed by comparing startle responses during prepulse and probe trials to those recorded in probe-alone trials using the following formula: $[(\text{Mean}_{\text{prepulse + probe}} - \text{Mean}_{\text{probe_alone}}) / (\text{Mean}_{\text{probe_alone}})] \times 100$. Thus, negative values represent PPI, and positive values indicate prepulse facilitation (PPF). We screened for outliers in each data collection session. If the percent prepulse modification for a rat was more than three times the interquartile range above the 75th percentile (Norusis, 1998) for all subjects, then the subject's data for that session were excluded (7.2%, 8.6%, 10.9%, and 3.1% of subjects' sessions were excluded from Experiments 1, 2, 3, and 4, respectively). Mean percent prepulse modification for each rat was averaged within condition (prepulse intensity in Experiment 1, SOA in Experiments 2–4) across the remaining sessions.

Percent prepulse modification was analyzed using an analysis of variance (ANOVA), with CS group (CS⁺ vs. CS⁰) as a between-subjects factor and prepulse intensity (Experiment 1) or SOA (Experiments 2–4) as a within-subject factor. Because these within-subjects factors involved more than two levels, Huynh–Feldt epsilon-adjusted degrees of freedom were employed to correct for violations of the assumption of sphericity (Huynh & Feldt, 1970; ϵ is reported instead of adjusted degrees of freedom). Significant interactions were probed with simple effects analyses. We used *t* tests to compare the two conditioning groups on probe-alone startle magnitude.

Conditioning

Method

Conditioning took place in the startle chambers and in two chambers that replicated the testing environment but did not contain potentiometers for measuring startle responses. To prevent the startle probe from disrupting acquisition, we gave each group 10 initial conditioning sessions of 60 trials each before introduction of the startle stimulus.

¹The between-subjects design used in this series of experiments differs from the procedures most often used with humans. A between-subjects design was used in this animal study because of the difficulty (caused by standing waves) of creating auditory prepulse stimuli that were distinguishable by the rats and were of equivalent perceived intensity within the confines of the startle testing boxes.

For the CS⁺ group, water was presented at the offset of the prepulse stimulus in 53 of the 60 trials. In 7 of the trials, the prepulse was presented without water presentation so that movement to the prepulse could be assessed across sessions without water presentation as a confounding variable. In the CS⁰ group, water presentation was uncorrelated with the prepulse and occurred at random intervals before, during, or after the prepulse. To enable water and prepulse presentation to be uncorrelated, water was presented according to a variable-interval 30-s schedule created using the method of Fleshler and Hoffman (1962). In addition, two separate orders were designed using separate schedules, and each rat was exposed to both orders to reduce the likelihood that any association between prepulse and water presentation would be made.

To assess the efficacy of the conditioning procedures, we examined movement data for trials in which water was not presented. We predicted that if rats in the CS⁺ group had learned to expect water after presentation of the prepulse, then they would exhibit greater movement than would CS⁰ rats around the time of CS offset. We examined mean movement (mV/ms) for trials in which water was not presented during Conditioning Sessions 1 and 10. Six half-second epochs (from 1 s before prepulse/CS onset to 1 s after prepulse/CS offset) were included in a 2 (group) × 2 (session) × 6 (epoch) ANOVA.

Results of Initial Conditioning

For the movement data during initial training, there was a statistically reliable Group × Session × Epoch linear interaction, $F(1, 14) = 14.6, p < .005$ (see Figure 1). During Session 1, there were no reliable group differences at any epoch ($F_s < 1.1$), demonstrating that the group differences did not exist prior to training. However, during Session 10 there was significantly greater movement in the CS⁺ group than in the CS⁰ group, beginning in the latter half of the prepulse (Epoch 4) and lasting throughout the postprepulse period (Epochs 5 and 6), $F_s(1, 14) = 8.0, 9.6, \text{ and } 15.4, p_s = .014, .008, \text{ and } .002$, respectively. These results suggest that the CS⁺ group learned the association between the prepulse stimulus and water. It is important to note that there was no evidence of differential movement between groups during the first 500 ms of prepulse presentation, $F(1, 14) = 1.3, p = .27$, which is the critical period for assessment of PPI.

Experiment 1

Method

In Experiment 1, prepulses were presented at a 120-ms SOA at three intensity levels (4, 7, and 10 dB above background). Prepulse intensity was randomized across trials within the session, and two counterbalanced orders were employed. Thirteen sessions of data collection were conducted.

Results

Figure 2 presents percent PPI for all Group × Prepulse Intensity conditions. As expected, the amount of PPI increased with increasing prepulse intensity $F(2, 28) = 22.4, p < .001$. Contrary to the attentional modification hypothesis but in keeping with a phasic dopamine response hypothesis, PPI tended to be reduced among the CS⁺ group in comparison with that seen in the CS⁰ group, $F(1, 14) = 4.1, p = .06$. Although the Group × Prepulse Intensity interaction was not statistically significant $F(2, 28) = 1.7, p < .20, \epsilon = 1.0$, post hoc tests suggested that the group difference was most apparent at the 10-dB intensity, group $F_s = 1.6, 3.4, \text{ and } 5.7, p_s < .22, .09, \text{ and } .03$ for the 4-, 7-, and 10-dB prepulse intensities, respectively.

There was a trend toward greater probe-alone startle magnitude in the CS⁰ group than in the CS⁺ group: means (SE) = 768 (98) and 515 (78), respectively, $t(14) = 2.0, p = .07$. Because the

group difference in PPI was most apparent with the 10-dB prepulse stimulus, this prepulse intensity was used for Experiments 2–4.

Experiment 2

Method

Experiment 2 was designed to test the time course of PPI modulation with the possibility that an attentional effect on PPI may occur more readily at a different time point in rats than does the typical 120 ms usually found with humans. Prepulse intensity remained constant at 10 dB above background and SOAs of 60-, 120-, and 800-ms were examined. Eight data collection sessions were conducted.

Results

Figure 3 presents percent PPI for all CS Group $\times$ SOA conditions. The group difference in PPI varied reliably across SOAs, $F(2, 28) = 10.6, p < .001, \epsilon = 1.0$. Follow-up tests indicated that there was a significant group difference at 60 ms, with the CS⁺ group again showing less PPI than the CS⁰ group, $F(1, 14) = 29.0, p < .001$. There was no reliable group difference at the 120- or 800-ms SOAs ($F_s < 1.5$). Probe-alone startle magnitude tended to be greater in the CS⁰ group than in the CS⁺ group, $t(14) = 1.8, p = .10$: CS⁰ $M = 766, SE = 110$ and CS⁺ $M = 522, SE = 86$.

Experiment 3

Method

Experiment 3 considered the time course of PPI in greater detail. The emphasis remained on the early part of the time course in which PPI is most typically examined, with 30-, 60-, 120-, 240-, 480-, and 950-ms SOAs tested. Prepulse intensity remained at 10 dB above background. Eight data collection sessions were conducted.

Results

Figure 4 presents percent PPI for all CS Group $\times$ SOA conditions. One rat (CS⁺ group) was excluded from the analysis because of extreme outlying data across several sessions. There was a significant CS Group $\times$ SOA interaction, $F(5, 65) = 3.5, p < .03, \epsilon = 0.58$. Follow-up tests indicated that the groups again differed at the 60-ms SOA, with the CS⁺ group showing less PPI than did the CS⁰ group, $F(1, 13) = 40.6, p < .001$. There was also a trend for greater startle facilitation at the 30-ms SOA in the CS⁺ group compared with that seen in the CS⁰ group, $F(1, 13) = 3.6, p < .08$. All other group comparisons were nonsignificant ($F_s < 1.7, p_s > .22$). The CS groups did not reliably differ on probe-alone startle magnitude, $t(13) = 1.5, p = .15$: CS⁰ $M = 783, SE = 118$, and CS⁺ $M = 547, SE = 98$.

Experiment 4

In Experiments 1–3, we found decreased PPI in the conditioned group. In Experiment 4, the CS conditions were reversed, with the original CS⁺ group receiving the water reward randomly (referred to as CS⁺/CS⁰) and the original CS⁰ group receiving water reward paired with each prepulse (referred to as CS⁰/CS⁺). Given the extensive prior training, a full reversal of any group differences was not expected. However, we expected that if group PPI and movement differences were indeed due to conditioning, then reversing the CS conditions across groups would reduce or eliminate the group differences that had been observed in Experiments 1–3.

Method

Prepulse intensity remained at 10 dB above background, and three SOAs were examined (30-, 60-, and 120-ms). Fourteen data collection sessions were conducted. Analysis of movement data from Experiment 4, similar to that of the initial conditioning analysis, was conducted to determine whether the reversal of the CS–water contingency between groups reversed or eliminated conditioned movement.

Results

Startle—Figure 5 illustrates the effects of the contingency reversal on PPI of startle. As expected given the extensive training the rats had experienced, the group difference in PPI did not fully reverse during this period. However, there was no longer a reliable difference in PPI between groups (CS Group and CS Group $\times$ SOA $F_s < 1$, $\epsilon = 0.76$), which is consistent with our prediction.

Another way to test the effect of the reversal manipulation is to compare PPI at the 60-ms SOA from Experiments 3 and 4. The results of a 2 (Group) $\times$ 2 (Experiment) ANOVA revealed a crossed interaction, $F(1, 13) = 9.9$, $p < .01$. As hypothesized, PPI tended to increase from Experiment 3 to Experiment 4 in the CS⁺/CS⁰ group, $F(1, 13) = 3.6$, $p = .08$, and PPI reliably decreased from Experiment 3 to Experiment 4 in the CS⁰/CS⁺ group, $F(1, 13) = 6.6$, $p < .03$. In Experiment 4, there was again a trend toward greater probe-alone startle magnitude in the CS⁰ group than in the CS⁺ group, $t(14) = 1.9$, $p = .08$: CS⁰/CS⁺ $M = 656$, $SE = 95$, and CS⁺/CS⁰ $M = 423$, $SE = 79$.

Further consideration of probe-alone magnitude across experiments—Two probe-alone magnitude issues emerged from this series of experiments and warranted further analysis. First, the means for probe-alone magnitude appeared to be smaller in Experiment 4 than in the other experiments. However, the results of an Experiment $\times$ Group ANOVA revealed no reliable differences in probe-alone startle magnitude across experiments (experiment and Experiment $\times$ Group, $F_s < 1$). Moreover, a specific contrast of Experiments 1–3 versus Experiment 4 provided the same results (experiment and Experiment $\times$ Group, $F_s < 1$).

Second, although we did not predict or anticipate that probe-alone magnitude would vary between the CS⁺ and CS⁰ groups in any experiment, this difference approached statistical significance in each of the experiments ($p_s = .07$, $.10$, $.15$, and $.08$ for Experiments 1–4, respectively). Furthermore, these effect sizes for these differences were large (Cohen's d [Cohen, 1988] = $.92$, $.82$, $.75$, and $.87$, for Experiments 1–4, respectively). Previous work has demonstrated that startle is inhibited during exposure to conditioned and unconditioned appetitive stimuli (e.g., Martin-Iverson & Stevenson, 2005; Schmid, Koch, & Schnitzler, 1995). By extension, it was possible that the overall experimental context was more pleasurable or appetitive for the CS⁺ group than for the CS⁰ group, though this was certainly not the intent or focus of the study. Most important, although percentage measures of PPI are generally relatively independent of probe-alone magnitude (e.g., Blumenthal, Elden, & Flaten, 2004; Ison, Bowen, Pak, & Gutierrez, 1997), it was possible that the group effect on PPI was due to the trends for reduced probe-alone magnitude in the CS⁺ group.

To determine whether probe-alone magnitude accounted for group differences in PPI, we reanalyzed the PPI data for each experiment, covarying probe-alone magnitude. In Experiment 1, in which only a 120-ms SOA was employed, covarying probe-alone magnitude reduced the group effect size from $.93$ to $.65$, but this difference continued to be a moderate-to-large effect (Cohen, 1988). In Experiments 2 and 3, the Group $\times$ SOA interactions remained reliable when probe-alone magnitude was covaried, and the large effect sizes for the group difference at the

60-ms SOA were minimally affected, with Cohen's d dropping from 1.59 to 1.47 in Experiment 2 and remaining completely unchanged ($d = 1.69$) in Experiment 3. Finally, recall that in Experiment 4, in which conditioning manipulation was reversed, the group difference in PPI was no longer reliable. Not surprisingly, covarying probe-alone magnitude had no effect on the pattern of findings. Overall, these supplemental analyses suggest that the observed trends towards group differences in probe-alone magnitude did not account for the effect of conditioning on PPI.

Conditioned movement postreversal—In Experiment 4, the CS condition was reversed for the two groups: The original conditioned group received uncorrelated presentations of prepulse and water (CS^+/CS^0), and the original control group received prepulse-water conditioning (CS^0/CS^+). As can be seen in Figure 6 (cf. Figure 1), the reversal influenced movement on prepulse-only, nonreinforced trials (trials included to examine movement uncontaminated by presentation of startle probes or water delivery), with statistically significant Group $\times$ Session $\times$ Epoch linear interactions and Group $\times$ Session $\times$ Epoch cubic interactions, $F_s(1, 14) = 6.6$ and 16.1 , $p_s < .030$ and $.005$, respectively. Follow-up tests demonstrated that by the final session of the experiment, the only reliable difference between the groups was enhanced movement in the first half-second after CS offset (Epoch 5, 2.0–2.5 s) in the CS^0/CS^+ group as compared with that seen in the CS^+/CS^0 group, $F(1, 14) = 57.6$, $p < .001$, which is consistent with the reversal nature of the design (cf., Figure 1). Among the CS^+/CS^0 group, an increase in movement during the last 1.5 s of the trial decreased from Session 1 to Session 14—Epochs 4–6 $F_s(1, 14) = 7.8, 7.0$, and 7.8 , $p_s < .02$, respectively—providing further evidence that the CS–water association was extinguished among the CS^+/CS^0 group. In the CS^0/CS^+ group, movement during the latter epochs emerged quickly in the reversal design (compare the top panel of Figure 6 with that of Figure 1), and the cubic trend grew more robust from Session 1 to Session 14, $F_s(1, 7) = 36.7$ and 246.6 , $p_s < .005$ and $.001$, respectively.

General Discussion

The goal of the present study was to develop an animal paradigm modeled after one used with humans (Dawson et al., 1993; Jennings et al., 1996; Schell et al., 2000) to assess the effects of controlled attentional processes on prepulse modification. To manipulate the salience of the prepulse, we conditioned one group of water-restricted rats to associate the white-noise prepulse with the presentation of a water reward (CS^+ group), whereas a second group was presented water at intervals that were explicitly not associated with the prepulse presentation (CS^0 group). Two alternative hypotheses were tested: an attentional model that predicted greater PPI among the CS^+ group than among the CS^0 group, and an appetitive cue model that predicted the opposite.

The movement data from the initial training sessions suggested that the conditioning was successful. By the end of training, the CS^+ group, but not the CS^0 group, demonstrated anticipatory movement during the latter half of the prestimulus (see Figure 1). It is important to note that this movement was not evident during the early part of the prestimulus presentation when most startle probes were presented. Thus, the movement data suggest that the conditioning procedure was effective but that the anticipatory movement observed in the CS^+ group did not confound the findings for short-lead PPI that were the primary focus of this series of studies.

The attentional hypothesis, derived from the human work, was that PPI would be increased for the rats that had the prepulse paired with a reward (CS^+) in comparison with the PPI for the rats that received the reward independently of the prepulse (CS^0). The opposite effect was found, with the CS^+ rats showing less PPI than did the CS^0 rats. In Experiment 1, the SOA was

set at 120 ms, when attentional modification of PPI is maximal in humans (e.g., Filion et al., 1993; Hawk et al., 2002). To test whether we had missed the typical human pattern of attentional modification with this SOA in rats, in Experiments 2 and 3, we examined PPI at SOAs ranging from 30 to 950 ms. We continued to observe reduced PPI in CS⁺ rats compared with that seen in CS⁰ rats, though at the 60-ms SOA rather than the 120-ms SOA.

Though not in line with our attentional hypothesis, the observed decrease in PPI is consistent with our alternative hypothesis, which predicted that PPI would be diminished in the CS⁺ group if the conditioned prepulses elicited a phasic release of mesolimbic dopamine. As outlined in the introduction, this prediction is based in extensive but separate literatures on the role of dopamine in reward and on dopaminergic substrates of PPI. The former literature suggests that with repeated pairings of the prepulse and water reward, the CS⁺ may have come to elicit a phasic release of dopamine soon after CS onset (Roitman, Wheeler, & Carelli, 2005; Romo & Schultz, 1990; Schultz, Dayan, & Montague, 1997). The literature on dopamine and PPI demonstrates that both the administration of dopamine agonists and infusion of dopamine into the nucleus accumbens decrease PPI (e.g., Feifel, 1999; Mansbach et al., 1988; Swerdlow et al., 1994) and that the time course of the effect of the indirect dopamine agonist amphetamine on accumbal dopamine overflow and PPI is parallel (Zhang, Forkstam, Engel, & Svensson, 2000).

Indeed, the apparent shift of the group difference from 120 ms (Experiment 1) to 60 ms (Experiments 2 and 3) can be related to the appetitive motivation model. For example, Schultz and his colleagues have conducted a series of studies in nonhuman primates in which activity in dopaminergic neurons in the ventral tegmentum is recorded during the presentation of food or juice rewards and cues that predict these rewards (e.g., Romo & Schultz, 1990; Schultz et al., 1997). Initially, reward delivery prompts a phasic increase in dopamine neuron activity. However, as conditioning continues, the brief increase in activity of these neurons shifts to occur soon after the presentation of the cue and no longer in response to the reward itself (Romo & Schultz, 1990; Schultz et al., 1997; Waelti, Dickinson, & Schultz, 2001).

Recent studies of the rapid time course of dopamine release with appetitive cues is generally consistent with our findings. Fast-scan cyclic voltammetry has demonstrated that food-related cues in both operant and Pavlovian studies elicit dopamine release within 100 to 300 ms of cue onset after just 9–12 training sessions (Day, Roitman, Wightman, & Carelli, in press; Roitman, Stuber, Phillips, Wightman, & Carelli, 2004). However, these dopaminergic responses to cues often persist and grow over hundreds of milliseconds. Thus, it is unclear why we would not continue to observe group differences at the 120-ms SOA in Experiments 2 and 3 if phasic dopamine release were driving the effects. It is possible that the time course of any cue-elicited dopamine response was speeded and shortened by the greater extent of the training, by the relative simplicity of the conditioning, and/or by the brief cue duration employed in the present study. However, it is clear that, at present, the dopamine account remains speculative, and it will be important to directly measure or manipulate dopaminergic activity in future research to better test this appetitive motivation model. It would also be useful to assess PPI during the conditioning phase to see if the shift in PPI coincides with conditioning.

Moreover, because PPI was not evaluated prior to conditioning, it is possible that the pattern observed in Experiments 1–3 could simply have reflected preexisting individual differences that occurred despite random assignment to conditioning group. To rule out this possibility, we reversed the conditioning for the two groups in Experiment 4. Although a full reversal of the PPI pattern between groups was not expected, given the extensive training prior to the reversal (39 sessions), both the PPI data and the movement in response to the CS suggest that the reversal manipulation did eliminate the differences between groups. That is, the movement data (see Figure 6) show extinction of CS-induced movement among the group in which the

CS originally predicted water delivery and shows the development of CS-induced movement in the other group once the CS predicted water delivery. With respect to PPI, two critical aspects of the data suggest the data were moving in the direction of a reversal. First, the group difference in PPI was no longer reliable once the contingencies were reversed. Second, as expected, statistical comparisons between Experiments 3 and 4 revealed that the reversal of contingencies tended to increase PPI in the CS⁺/CS⁰ group and to decrease PPI in the CS⁰/CS⁺ group. Overall, these findings are consistent with a conditioning interpretation and inconsistent with a hypothesis of preexisting group differences in PPI. Thus, the data from Experiments 1–4 suggest that appetitive prepulses reduce, rather than enhance, PPI in rats.²

Although the present data are consistent with the literature on conditioned reinforcement, they directly oppose the prediction derived from an attentional perspective in the human literature and in recent, preliminary animal work (Röskam & Koch, 2006). With respect to the animal findings, the current study differed from that of Röskam and Koch in several potentially important methodological details, including species of rat and modality of the prepulse. In addition, as Röskam and Koch acknowledge, their paradigm led them to consider only a 300-ms SOA. This SOA is outside the typical range in the human and animal PPI literatures, and somewhat different processes may be operating there. Finally, the two methodologies examine very different types of motivation. In Röskam and Koch (2006), the conditioned inhibitor was believed to reduce defensive motivation, whereas the CS⁺ in the present study was designed to enhance appetitive motivation.³ Unfortunately, considerably more work must be done in this area to determine the parameters that reliably influence these effects. Given the potential of PPI as a cross-species translational paradigm, that work is clearly warranted. The difference in findings between the present work on appetitive motivation and the recent report of Röskam and Koch (2006) with defensive motivation suggests that consideration of both types of salient stimuli will also be important.

In turning to comparisons of the present study with the human literature on attentional modification, we raise two further considerations regarding the current findings of reduced PPI among rats receiving the prestimuli paired with water delivery as compared with rats who received uncorrelated presentations of prestimuli and water. First, one potentially important difference between the present conditioning paradigm and the tone-discrimination paradigm employed in human studies is the nature of the attention manipulation. In human studies, participants are usually asked to listen to tones of two differing pitches and are provided a performance-based monetary incentive to discriminate the duration of prepulses of one pitch while ignoring prepulses of the other pitch. PPI for attended and ignored prepulses is then compared within subjects. In the present study, attention was directed to the prepulse by making

²An alternative interpretation is that the results reflect group differences in short-lead PPF, rather than differences in PPI. In rats, prestimuli, including modest increases in ambient white noise, facilitate the magnitude of the startle response at SOAs up to 40 ms (e.g., Ison, Taylor, Bowen, & Schwarzkopf, 1997; Reijmers & Peeters, 1994). Indeed, PPF was observed for the 30-ms SOA in Experiments 3 and 4 (see Figures 5 and 6). Short-lead PPF and PPI may reflect distinct processes, and the ultimate magnitude of the startle response may be a summation of these processes (see Ison et al., 1997). Therefore, it is possible that the present results were due to an enhancement of PPF, rather than a reduction of PPI, among the CS⁺ group relative to the CS⁰ group. However, two aspects of the current data argue against this interpretation. First, short-lead PPF peaks within the 10- to 30-ms range in rats. If PPF were driving the group difference, then the difference would be most evident at the 30-ms SOA. However, the effect was robust at the 60-ms SOA (Experiments 2 and 3) and was only marginally statistically significant at the 30-ms SOA (Experiment 3). Second, short-lead PPF is most evident with increases in background noise that are very near threshold (e.g., 3 dB); short-lead PPF is weaker or nonexistent with the 10-dB increases used in most of the present work (e.g., Ison et al., 1997; Reijmers & Peeters, 1994). Indeed, if anything, the reduction of PPI in the CS⁺ group was most apparent with prestimuli 10 dB above background, relative to weaker prestimuli (Experiment 1). Thus, it appears that the present results most likely reflect differences in PPI rather than PPF.

³Although deprivation from natural reinforcers can produce a state of “frustrative nonreward” that may potentiate startle responding in humans when the reinforcer is unavailable (Drobes, Miller, Hillman, Bradley, Cuthbert, & Lang, 2001), appetitive motivation appears to be fostered when the reinforcer is available, inhibiting startle (Hawk et al., 2004). Similarly, prior work in rats demonstrates that cues for both food and brain stimulation reward inhibit startle at long SOAs, consistent with a “pleasure-attenuated startle” interpretation (Schmid et al., 1995; Steidl, Li, & Yeomans, 2001). Thus, the CS⁺ in the present work seems quite likely to be engaging appetitive motivation.

the prepulse stimulus motivationally relevant or irrelevant, and PPI was compared between subjects. Thus, human participants need to actively make a discrimination about some characteristic of the to-be-attended prepulse (e.g., Filion et al., 1993), whereas for the rats in this study, the prepulse is either relevant or irrelevant in respect to the presentation of a reward and no discrimination is required. It may be that both attention and appetitive motivation processes are components of both tasks but that greater attentional resources are engaged in the discrimination task. To address the possibility that the current paradigm required little attentional processing by the rats in the attend group, future studies could incorporate a discrimination task in which rats in the attend condition need to make a discrimination of the duration (or some other characteristic) of the prepulse in order to receive the reward. This would also provide an independent measure of attention, which was lacking in the present work.

Nonetheless, reduced attentional engagement in the conditioning procedure would lead to equivalent PPI between the CS⁺ and CS⁰ groups and not to reduced PPI in the CS⁺ group. The only way an attentional account could accommodate the present findings would be to suggest that the conditioning actually reduced attention to the prepulse. This prediction seems relatively untenable, given that appetitive stimuli should grab our attention (e.g., Lang et al., 1997) and that attentional modification is enhanced by performance-based incentives in humans (Hawk et al., 2002). Still, the incorporation of a discrimination component into the rat paradigm would be helpful for disconfirming an attention-reduction hypothesis. It may also prove useful to include a control group that does not experience water deprivation or water delivery, analogous to a no-task group in human studies (e.g., Filion & Poje, 2003).

A second major difference between the present rat work and the typical human study is the temporal relationship between the prestimuli and the rewards to which they were related. Human participants typically receive no feedback or other reinforcement from trial to trial; they are informed of their performance after completion of the entire task. In contrast, the present conditioning procedure provided perfectly reliable trial-by-trial consequences for the CS⁺. Stated differently, the prepulse became a conditioned reinforcer.

Of course, the appetitive motivation hypothesis is speculative at this point given that we did not directly measure dopamine responding. Converging evidence should be sought in both rats and humans. Regarding the former, we would predict that dopamine antagonists should restore PPI in the CS⁺ group to a level comparable with that of the CS⁰ group in rats. In humans, PPI is reduced in the presence of craved in vivo food and drug cues (Hawk, Baschnagel, Ashare, & Epstein, 2004; Hutchison, Niaura, & Swift, 1999). There is also some evidence that dopamine agonists reduce PPI in humans (e.g., Giakoumaki, Roussos, Frangou, & Bitsios, in press; Hutchison & Swift, 1999), though this reduction is not as reliable as in rats (see Swerdlow, Stephany, et al., 2002, 2003) and may only be evident among participants with relatively high levels of PPI at baseline (e.g., Bitsios, Giakoumaki, & Frangou, 2005; Swerdlow et al., 2003). These cue and pharmacologic findings are broadly consistent with an appetitive, dopaminergic account. However, the appetitive cue and pharmacologic work have not been brought together in human work to date.

The current study suggests a methodology for moving in that direction and, at a more basic level, provides a model for examining motivated attention in humans. Although much of the work to date has involved performance-based monetary incentives, these incentives have been distal, with no trial-by-trial consequences. In a recent within-subjects study of young adults completing the tone-discrimination paradigm, we found that monetary incentives with trialwise feedback increased attentional modification of PPI relative to that seen in a try-your-best condition (Ashare et al., in press). However, the motivational salience of that incentive, which was up to \$10 for the entire session, remained modest in comparison with the water

unconditioned stimulus (UCS) used with water-deprived animals in the present study. It may be more comparable to the use of a food reinforcer among food-deprived human participants. Moreover, although performance feedback was given on each trial in the incentive condition, money was not provided until the end of the study. Finally, the number of trials is typically very modest in the human work, and it would be interesting to determine whether there would be a shift from enhanced PPI to reduced PPI in relation to proximal, large-magnitude rewards across repeated testing sessions. Alternatively, moving from the operant framework, it will be intriguing to examine the effects of an appetitive Pavlovian CS^+ and CS^0 in humans.

Still, given that the results of this study were opposite of those predicted from the human attentional-modification literature and preliminary data from animals (Röskam & Koch, 2006), we cannot yet move forward with using this paradigm to test drug effects on controlled attentional processes or models of attention deficits in psychopathology. The current findings show that biologically salient appetitive prepulses presented to rats do not have the same effect that attended prepulses have on PPI in humans. If we are to move forward in developing an animal model of attentional modification, it will be important to minimize mesolimbic dopamine responses, which appear to reduce PPI, relative to attentional processing, which appears in humans to enhance PPI. The incorporation of a discrimination component and introduction of a lean reinforcement schedule, in which the CS^+ is only intermittently or weakly reinforced, may yield results that are more parallel to the existing human work on attentional modification of PPI. Alternatively, borrowing from Röskam and Koch's (2006) work on defensive motivation, the use of a conditioned inhibitor of appetitive motivation may be fruitful. For example, in Pavlovian conditioning with monkeys, a visual conditioned inhibitor eliminated anticipatory approach behavior and markedly attenuated the phasic increase in firing of midbrain dopamine neurons elicited by an appetitive CS^+ alone (Tobler, Dickinson, & Schultz, 2003). Ultimately, the success of any given approach may be tied, at least in part, to its ability to engage the prefrontal cortex, known to be important in attention and PPI (e.g., Hazlett et al., 2001; Sarter, Gehring, & Kozak, 2006; Swerdlow et al., 2001) and capable of modulating phasic mesolimbic dopamine responses (e.g., Bilder, Volavka, Lachman, & Grace, 2004; see also Bitsios et al., 2005).

Thus, the current findings suggest additional interesting avenues of investigation. If the dopamine hypothesis is not rejected in attempts to replicate and extend the present work, then future animal models of attentional modification of PPI will need to develop approaches that preferentially increase attentional processing relative to reward or incentive responses. Conversely, PPI may provide a useful cross-species model for examining reactivity to drug cues and to the incentive salience of other motivationally relevant stimuli (Hawk et al., 2004). More broadly, the present study highlights the need for further work that precisely links the human and animal PPI literatures and that simultaneously considers both attention and motivation.

Acknowledgements

A portion of this work was presented as a poster at the 2004 Annual Meeting of the Society for Neuroscience in San Diego, CA. This research was funded by an Interdisciplinary Research and Creative Activities Fund grant from the University at Buffalo to Larry W. Hawk, Jr. (primary investigator), Craig R. Colder, and Jerry B. Richards and by Grant DA10588 to Jerry B. Richards. Preparation of this article was supported in part by Grant MH069434 to Larry W. Hawk, Jr. (primary investigator), Jerry B. Richards, and Craig R. Colder. We would like to thank Art Kieres, Andy Farar, Kathy Hausknecht, Ashley Acheson, Seulgi Choi, Veronica Peterson, and Michele Patak for their assistance with data collection and thank Rebecca Ashare, Keri Shiels, and Brady Reynolds for comments on an earlier draft of the article.

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Conditioning Session 1 **Conditioning Session 10**

Figure 1. Mean movement for all Group $\times$ Epoch (500 ms) conditions during Conditioning Sessions 1 (upper panel) and 10 (lower panel). CS = conditioned stimulus. Bars are standard error.

Figure 2. Mean percent prepulse modification for all Group $\times$ Prepulse Intensity conditions in Experiment 1. CS⁺ = group conditioned to associate prepulse with water; CS⁰ = group given water independent of the prepulse. Bars are standard error.

Figure 3. Mean percent prepulse inhibition for all Group $\times$ Stimulus Onset Asynchronies (SOA) conditions in Experiment 2. CS⁺ = group conditioned to associate prepulse with water; CS⁰ = group given water independent of the prepulse. Bars are standard error.

Figure 4. Mean percent prepulse inhibition for all Group $\times$ Stimulus Onset Asynchronies (SOA) conditions in Experiment 3. CS⁺ = group conditioned to associate prepulse with water; CS⁰ = group given water independent of the prepulse. Bars are standard error.

Figure 5.

Mean percent prepulse inhibition for all Group $\times$ Stimulus Onset Asynchronies (SOA) conditions in Experiment 4. CS⁺ = group conditioned to associate prepulse with water; CS⁰ = group given water independent of the prepulse. Bars are standard error.

Session 1

Session 14

Figure 6. Conditioned movement after reversal. Mean movement for all Group $\times$ Epoch (500 ms) conditions during Sessions 1 (upper panel) and 14 (lower panel) of Experiment 4. Bars represent standard error.