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Effects of prepulse intensity, duration, and bandwidth on perceived intensity of startling acoustic stimuli

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Abstract

Intense abrupt stimuli can elicit a startle reflex; a weak “prepulse” 30–300 ms earlier can reduce both startle and perceived stimulus intensity. Prepulse inhibition (PPI) of startle, an operational measure of sensorimotor gating, is used to understand brain disorders characterized by gating deficits. Compared to startle, PPI of perceived stimulus intensity (PPIPSI) may provide information that is distinct, and easier to acquire and analyze. To develop this experimental measure, we examined PPIPSI under different stimulus conditions. Both PPI and PPIPSI exhibited a non-linear relationship to prepulse intensity, with prepulses 15 dB(A) above background causing maximal inhibition of both measures. Fifty ms broadband noise prepulses produced maximal PPI and PPIPSI, whereas 5 and 20 ms pure tone prepulses produced maximal PPIPSI and PPI, respectively. PPIPSI is a robust, parametrically sensitive and “low tech” measure of sensory gating that may become a valuable tool for understanding the biology of certain mental disorders.

Keywords

prepulse inhibition; perception; sensorimotor gating

Introduction

Several neuropsychiatric disorders are clinically characterized by a failure to automatically suppress or “gate” unwanted or uninformative sensory information (McGhie & Chapman 1961; Braff et al., 1982; Cohen & Leckman 1992; Leckman et al., 1993; Miguel et al., 2000). Some experimental paradigms have proven useful for studying the neurobiology and genetics of these gating deficits. In prepulse inhibition of startle (PPI: Graham 1975), weak lead stimuli inhibit the motor response to intense, abrupt acoustic, tactile, or visual stimuli. PPI is an operational measure of sensorimotor gating: the prepulse is thought to activate time-linked inhibitory neural processes that blunt the motor response to stimuli in its immediate aftermath. PPI is reduced in schizophrenia (Braff et al., 1978) and several other neuropsychiatric disorders

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A fast-rising tone, as was used in Exp. 2, has a very brief (less than 5 ms) broadband “noise-like” component at its onset, a phenomenon known as frequency splatter (Berg & Balaban, 1999). This decreases the difference between noise and tone stimuli in their initial component, although the tone quickly acquires its expected sine wave form. Therefore, differences in the impact of noise and tone will tend to be attenuated when fast rise times are used, so bandwidth effects that are found can be considered to be slightly more powerful than would be the case with a ramped onset tone.

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(cf. Braff et al., 2001b), and this deficit is being used as an endophenotype for identifying genes for these disorders (cf. Braff & Freedman, 2002).

A more direct measurement of sensory gating was first reported by Helen Peak in 1939 (Peak 1939), and has been described as “prepulse inhibition of perceived stimulus intensity” (PPIPSI) (Swerdlow et al., 2002,2005). PPIPSI is derived from the direct report of the perceived intensity of a probe stimulus, in the presence or absence of a prestimulus. This form of cross-modal magnitude estimation is an established and reliable psychophysical procedure (cf. Hellman 1999). Under appropriate stimulus conditions, participants report that they perceive an intense abrupt stimulus, e.g. a 118 dB(A) noise burst (Swerdlow et al., 1999), a 40 psi air puff (Swerdlow et al., 1999), or a 170 V cutaneous shock (Blumenthal et al., 2001), to be less intense if it is preceded by a weak prepulse. A similar process, loudness assimilation, occurs when two sounds of different intensities are “averaged” when they occur closer together in time (Elmasian, Galambos, & Bernheim, 1980). However, PPIPSI probably involves the activation of an inhibitory process by the prepulse, rather than being due to loudness assimilation, due the fact that this inhibition of loudness occurs across sensory modalities (Swerdlow et al., 1999). Perceived stimulus intensity and its inhibition by prepulses are easy to measure, exhibit minimal variability and strong test-retest stability, and can be used to evaluate psychiatrically relevant issues (Swerdlow et al., 1999;2002;2005). For example, we previously reported that PPIPSI required lead intervals of at least 60 ms between prepulse onset and startle stimulus onset, suggesting that, unlike PPI of startle, it required the engagement of attentionally-sensitive mechanisms (Swerdlow et al., 2005). Although PPI of startle and PPIPSI both occur on a given trial, a researcher could measure one without the other. Both are dependent on ascending sensory input and the activation of an inhibitory mechanism, but they diverge in the fact that PPI is based on midbrain and brainstem mechanisms, whereas PPIPSI requires a higher cognitive evaluation of the stimulus combination. Therefore, PPIPSI may be closer to a real-life evaluation of the perceptual experience of the subject, and, therefore, of the problems of this experience in patients with certain clinical diagnoses.

To facilitate the use of PPIPSI to study sensory gating in normal and disordered populations, it will be important to understand its sensitivity to experimental conditions, particularly stimulus parameters, and to identify those parameters that will generate the most robust levels of PPIPSI. Similar parametric studies of PPI have proven invaluable in the process of studying and applying that measure of sensorimotor gating (cf. Braff et al., 2001b). In the present study, we assessed the relationship between PPIPSI and prepulse intensity, duration, and bandwidth. To the extent that PPIPSI provides information similar to that found with PPI of startle, we expected increased PPIPSI as prepulse intensity or duration increased to some asymptote (Blumenthal, 1995,1996), and greater PPIPSI with broadband noise prepulses than with pure tone prepulses (Wynn et al., 2000).

Experimental Methods

Participants

Methods were approved by the UCSD Institutional Review Board, and approved and supported by NIMH 59803. Forty people participated across two experiments (M:F = 17:23; age mean (range, y) = 23.30 (18-33); years education mean (range, y) = 15.20 (12-20); ethnicity - Caucasian: Asian: Hispanic: African American: Other = 12:19: 6: 1: 2). Phone screening and in-person interviews (SCID-NP (First et al., 1997)) excluded individuals with mental illness or drug abuse histories. No participants demonstrated hearing impairment (> 40 dB(A) at 1000 Hz using an Audiometrics Audiometer (Assens, Denmark) and hearing threshold using methods of ascending and descending limits) or positive urine toxicology screens.

Apparatus

Stimuli were delivered by Telephonics (TDH-39-P, Maico) headphones. Two Ag/AgCl electrodes (In Vivo Metric) were positioned below and to the outer canthus of each eye over the orbicularis oculi facial muscles, with a ground electrode behind the right ear over the mastoid muscle (impedance < 10 kOhm). Eyeblink was measured by EMG activity (San Diego Instruments) that was band-pass filtered (1-1000 Hz) and 60-Hz notch filtered, then digitized, and 250 1-ms readings were recorded starting at startle stimulus onset (EMG sensitivity 1.22 μ V/unit). Resting EMG activity was recorded between startle trials (“nostim”), in which the recording window was activated for 250 ms but no stimulus was delivered.

Procedure

During testing, participants sat upright, looked straight ahead, and were instructed to stay awake. Participants held a custom-built 20 cm $\times$ 7.5 cm $\times$ 3 cm visual analog scale (VAS) slider with a 10 cm slit along which they could move a lever on the surface of the slider. They held the slider approximately 30 cm from their body, and they sat approximately 60 cm in front of a computer screen (Dell, model E151FPb) containing a 17.5 cm wide image resembling the top of the slider box. Movement of the slider led to a corresponding movement in the computer image. They were instructed that the left end of the line on the screen corresponded to “not loud,” and the right end corresponded to “loud”. After each stimulus, participants used their non-dominant hand to move the slider to a position that corresponded to their perceived intensity of the stimulus, and to press a button on the slider box to record their rating on the computer. The instructions did not distinguish the prepulse from the pulse stimuli, so that the subjective ratings (like the motor response) reflected the compound stimulus (prepulse + pulse) on prepulse trials. This procedure of computerized VAS rating has been shown to yield VAS scores with a near perfect correspondence to verbally-reported scores (Stephany et al., 2003).

A background 70 dB(A) white noise continued throughout each test session and was followed 3 min after onset by the startle trials. Two types of test session were used, with different participants:

Experiment 1—The “Intensity Session” (n=20; M:F=7:13) began and ended with a series of 5 “pulse alone” (PA) trials on which a 90, 95, 100, 105, or 110 dB(A) 40 ms noise burst was presented alone (PA90, PA95, PA100, PA105, PA110). Between these blocks were 36 trials on which the PA105 was either presented alone or preceded by 120 ms (onset-to-onset) by a 20 ms noise burst that was 15, 20, 25, 30, or 35 dB(A) over background (PP15, PP20, PP25, PP30, PP35), with 6 repetitions each of PA105, PP15, PP20, PP25, PP30, and PP35, in pseudorandom order. All stimuli had fast rise and fall times (< 1 ms). Variable intertrial intervals averaged 11.5 s (9 - 13 s).

Experiment 2—The “Prepulse Duration and Bandwidth Session (n=20; M:F=10:10)” began and ended with a series of 5 “pulse alone” (PA) trials on which a 90, 95, 100, 105, or 110 dB (A) 40 ms noise burst was presented alone (PA90, PA95, PA100, PA105, PA110). Between these blocks were 81 trials on which the PA105 was either presented alone or preceded by 120 ms (onset-to-onset) by either a 16 dB(A) over background white noise (WN) or 1000 Hz pure tone (PT) of 5, 20, 50 or 120 ms duration (WN5, WN20, WN50, WN120, or PT5, PT20, PT50, PT120), with 9 repetitions each of PA105, WN5, WN20, WN50, WN120, PT5, PT20, PT50, and PT120, in pseudorandom order. All stimuli had fast rise and fall times (< 1 ms)¹. Variable intertrial intervals averaged 11 s (10 - 12 s).

The choice of stimulus parameters reflected: 1) previous evidence of maximal PPIPSI with 105 dB(A) white noise pulses (Swerdlow et al., 1999), and 2) previous findings of robust PPIPSI using 20 ms prepulses 12-16 dB(A) over background, with PPIPSI for 16 dB(A) over

background prepulses significantly greater than for 12 dB(A) over background prepulses (Swerdlow et al., 2002,2005). Thus, both of the present sessions utilized 105 dB(A) white noise pulses, and the intensity session used 15 dB(A) over background as its lowest intensity (since the intensity function between 12-16 dB(A) over background is known to be ascending).

PPI was defined as $(100 - [100 \times \text{magnitude on prepulse trial} / \text{magnitude on pulse alone trial}])$. No consistent differences were noted between right and left eye measures, and thus main effects of eye side and interactions are not reported. VAS scores (in mm) were treated as raw (non-transformed) data. These data were also “range-corrected” so that each PPIPSI value was expressed as a fraction of the range (max minus min) of pulse alone ratings for that participant $[100 \times (\text{VAS on pulse alone trial} - \text{VAS on prepulse trial}) / \text{VAS range on pulse alone trials}]$ (Swerdlow et al., 1999;2002;2005). Due to the relatively weak startle pulse (35 dB(A) over background), several test participants exhibited minimal or no startle responses to pulse alone trials; 13 participants whose mean startle value on these trials was < 10 units (12.2 μV) were categorized as “non-responders”, and their data were included in analyses of VAS and %PPIPSI ($n=40$), but were excluded from analysis of %PPI ($n=27$) (“non-responders” did not differ significantly from “responders” in hearing threshold). PPI and PPIPSI data were analyzed by repeated-measure ANOVA with Greenhouse-Geisser corrections. Alpha was 0.05. This study was not designed to assess sex differences in sensitivity to the different prepulse types or test specific hypotheses in this regard; thus, sex was not used as a grouping factor in the ANOVA design.

ANOVAs in Experiment 1 were structured using within-subject factors of “trial type” for raw data (of PA105, PP15, PP20, PP25, PP30 or PP35) and “prepulse intensity” (15, 20, 25, 30 or 35 dB(A) over background) for percent data. ANOVAs in Experiment 2 were structured using within-subject factors of “trial type” for raw data (two separate ANOVAs for: 1) PA105, WN5, WN20, WN50, WN120; and 2) PA105, PT5, PT20, PT50, and PT120), and “prepulse duration” (5, 20, 50 or 120 ms) and bandwidth (PT or WN) for percent data.

Results

Experiment 1

The relationship between VAS ratings, PPIPSI and prepulse intensity are seen in Figure 1A-B. ANOVA of raw VAS scores revealed a significant effect of trial type ($F(5,95) = 15.37$, $p < 0.0001$; $h_p^2 = 0.45$) (Figure 1A). Compared to pulse alone trials, VAS ratings were reduced on trials with prepulses that were 15, 20 or 25 dB(A) over background ($p < 0.0001$, $d > 0.34$, all comparisons), but not on trials with more intense prepulses. ANOVA of %PPIPSI (range-corrected) confirmed a significant main effect of prepulse intensity ($F(4,76) = 15.38$, $p < 0.0001$; $h_p^2 = 0.44$) (Figure 1B). Maximal loudness inhibition was evident with 15 dB(A) over background prepulses. Based on the intensity functions assessed during the test session (Figure 1A, inset), this change represents an effective reduction of approximately 2.33 dB(A).

Results of startle measures during this intensity session are seen in Figure 1C. Because of the use of weak startle stimuli relative to background noise, 7 out of 20 (35%; M:F = 3:4) of the participants exhibited mean startle magnitude < 10 units on pulse alone trials, and thus their PPI data were not analyzed; comparisons of VAS and %PPIPSI data between startle “responders” and “non-responders” revealed no significant main or interaction effects.

Among the 13 startle “responders” (M:F = 4:9), ANOVA of startle magnitude across all trials revealed a significant effect of trial type ($F(5,60) = 23.79$, $p < 0.0001$; $h_p^2 = 0.66$). In contrast to VAS ratings, startle magnitude was significantly reduced at all prepulse intensities; maximal inhibition (essentially full reflex suppression) was seen with the weakest prepulses (15-20 dB

(A) over background), with more intense prepulses eliciting less startle inhibition ($p < 0.0001$, $d > 0.92$ for 15-30 dB(A) over background prepulses, and $p < 0.0002$, $d = 0.50$ for 35 dB(A) over background prepulses). Consistent with this, ANOVA of %PPI revealed a significant effect of prepulse intensity ($F(4,48) = 25.88$, $p < 0.0001$; $h_p^2 = 0.68$) (Figure 1D).

Experiment 2

The relationships between VAS, PPIPSI and prepulse duration and bandwidth are seen in Figure 2A-B. Because the pulse alone trial was used for assessing PPIPSI with both white noise and pure tone prepulses, separate ANOVAs of raw VAS were conducted for the two prepulse bandwidths. ANOVA of VAS with white noise prepulses revealed a significant effect of trial type ($F(4,76) = 18.71$, $p < 0.0001$; $h_p^2 = 0.50$), as did ANOVA of VAS with pure tone prepulses ($F(4,76) = 14.64$, $p < 0.0001$; $h_p^2 = 0.44$) (Figure 2A). For white noise prepulses, PPIPSI increased with increasing prepulse duration up to 50 ms, while with pure tone prepulses, PPIPSI was maximal with the shortest prepulses (5 ms), and diminished with increasing prepulse duration. In contrast to shorter prepulses, 120 ms tone prepulses significantly enhanced perceived intensity ($p < 0.015$; $d = 0.20$).

Consistent with these separate analyses of raw VAS scores, ANOVA of %PPIPSI (range corrected) revealed an overall significant effect of prepulse duration ($F(3,57) = 29.52$, $p < 0.0001$; $h_p^2 = 0.61$), a significant effect of prepulse bandwidth ($F(1,19) = 4.90$, $p < 0.04$; $h_p^2 = 0.21$), and a significant interaction of prepulse bandwidth $\times$ duration ($F(3,57) = 5.51$, $p < 0.003$; $h_p^2 = 0.22$) (Figure 2B). Separate post hoc analyses in trials with noise and tone prepulses each revealed significant effects of prepulse duration ($p < 0.0001$, both comparisons; $h_p^2 = 0.56$ and 0.49 , respectively). Patterns of %PPIPSI followed those described above for raw VAS scores; the effects of bandwidth reflected more loudness inhibition with white noise vs. pure tone prepulses, particularly at the middle prepulse durations (20-50 ms). Maximal % PPIPSI was seen at 50 ms for noise prepulses and 5 ms for tone prepulses. Based on the intensity functions assessed during the test session (Figure 2A, inset), these changes represent an effective reduction of 1.84 dB(A) for noise prepulses and 1.61 dB(A) for tone prepulses.

Results of startle testing during this session are seen in Figure 2C. Again, because of the use of weak startle stimuli relative to background noise, 6 out of 20 (30%; M:F = 4:2) of the participants exhibited mean startle magnitude < 10 units on pulse alone trials, and thus their PPI data were not analyzed. As with the intensity session, inspection of VAS scores in this session revealed no clear distinction between startle “responders” vs. “non-responders”. Among the 14 startle “responders” (M:F = 6:8), ANOVA of startle magnitude for pulse alone and noise prepulse trials revealed a significant effect of trial type ($F(4,52) = 17.08$, $p < 0.0001$; $h_p^2 = 0.57$). Post-hoc comparisons revealed significant reflex inhibition with all prepulse durations, compared to pulse alone startle magnitude. ANOVA of startle magnitude for pulse alone and tone noise prepulse trials revealed a significant effect of trial type ($F(4,52) = 14.02$, $p < 0.0001$; $h_p^2 = 0.52$). Post-hoc comparisons again revealed significant reflex inhibition with all prepulse durations, compared to pulse alone startle magnitude (Figure 2C).

Consistent with this, ANOVA of %PPI revealed significant effects of prepulse bandwidth ($F(1,13) = 5.71$, $p < 0.035$; $h_p^2 = 0.31$) and duration ($F(3,39) = 4.28$, $p = 0.01$; $h_p^2 = 0.25$), and no interaction of bandwidth $\times$ duration ($F(3,39) = 1.60$, ns). This lack of statistical interaction reflects the relatively similar impact of prepulse duration on %PPI with WN and PT prepulses

(see Figure 2D; contrast with Figure 2B for %PPIPSI), though inspection of the data revealed maximal PPI with 50 ms prepulse duration for noise prepulses, and 20 ms duration for tones.

Discussion

This study identified several relationships between prepulse characteristics and their ability to inhibit perceived stimulus intensity. Maximal perceptual inhibition was elicited by noise prepulses that were 15 dB(A) over background, and by prepulses of 50 ms duration if they were white noise, and 5 ms duration if they were pure tones. Levels of maximal effective inhibition by white noise and pure tone prepulses were roughly comparable: approximately 15-20%. This study also demonstrated that PPIPSI could be efficiently measured with an automated VAS computer interface, with clear parametric sensitivity, and relatively low variability (compare SEM bars for VAS and startle measures in Figures 1A vs. 1C, and 2A vs. 2C).

Our previous studies demonstrated maximal effective inhibition with 105 dB(A) noise pulses vs. weaker or more intense pulses, with 16 dB(A) over background vs. weaker prepulse intensities, and with 100 - 120 ms lead intervals vs. shorter intervals, using test sessions that were otherwise structurally similar to the present “intensity session” (i.e. 70 dB(A) background and 20 ms white noise prepulses) (Swerdlow et al., 1999,2002,2005). Many other test parameters might modify PPIPSI (e.g. background noise level, startle pulse duration); indeed, the stimulus conditions used as a starting point for empirical assessment in the present study, and in previous studies of PPIPSI, were taken from studies of PPI, to permit an empirical test of the link between these two conceptually-related measures. One might argue that measures of PPIPSI would be most informative with stimuli that are incompatible with the measurement of startle or PPI, although in previous studies (Swerdlow et al., 1999,2005), a substantial range was tested for each of the stimulus parameters (including non-startling stimuli, and ones that do not produce PPI), to arrive at the “optimal” conditions for assessing PPIPSI. Thus, while entirely different types of stimuli and experimental conditions might provide greater sensitivity, under conditions common to our laboratory and many others, maximal PPIPSI is achieved using noise burst prepulses, 15-16 dB(A) over background, 50 ms in duration, with prepulse onset 100 - 120 ms prior to the onset of 105 dB(A) noise bursts. These parameters would seem to be optimal for studies where a large PPIPSI effect is desired, such as studies using PPIPSI as a potential endophenotype for identifying genes, or as a biomarker for drug studies.

As reported previously, there were similarities and differences in prepulse effects on perceptual and motor inhibition. Parallel stimulus functions were evident in VAS rating and startle magnitude, and in %PPIPSI and %PPI, as can be appreciated by comparing Figures 1A vs. 1C, 1B vs. 1D, 2A vs. 2C and 2B vs. 2D. However, closer inspection reveals clear differences in both pulse and prepulse effects on perceptual vs. motor processes. For example, maximal motor inhibition approached 100% in these studies, while maximal perceptual inhibition approached only 20%; similar findings have been reported by our group (Swerdlow et al., 1999,2002,2005) and others (Cohen et al., 1981; Perlstein et al., 1993; Peak 1939). Some prestimuli elicited no perceptual inhibition, despite eliciting substantial reflex inhibition: in the “intensity session”, prepulses of 30-35 dB(A) over background intensity elicited no perceptual inhibition, but inhibited startle magnitude by 50-60%. In some cases, different prepulse stimuli elicited identical levels of motor inhibition (e.g. PPI with 50 ms noise vs. tone prepulses; Figure 2D), but very different levels of perceptual inhibition (e.g. PPIPSI with 50 ms noise vs. tone prepulses: noise > pure tone, $F(1,19) = 11.71$, $p < 0.003$; Figure 2B).

Consistent with previous reports (e.g. Braff et al., 2001a), continuous 120 ms tone prepulses inhibited startle magnitude by 50-60%. Knowledge that these prepulses would inhibit the

startling impact of pulses was the motivation for empirically testing their impact on the perceived intensity of these pulses. In contrast to their effects on startle, these prepulses augmented the perceived intensity of the startle stimulus. Continuous prepulses terminate at the moment that the startle stimulus begins, suggesting that participants may have been judging the loudness of a single composite stimulus, rather than restricting their judgment to the startle probe alone. In all other prepulse conditions, there was a gap between prepulse offset and startle stimulus onset that was sufficient to distinguish the two stimuli from each other. More generally, the fact that, above certain thresholds, greater prepulse intensity or duration is associated with less PPIPSI suggests that prepulses activate opposing processes, such as perceptual inhibition and summation. Loudness ratings reflect the perceived intensity of the compound stimulus that includes the prepulse and pulse; above certain thresholds, the salience of the prepulse summates with the pulse, and the compound stimulus is perceived to have a greater total intensity. This “binding threshold” appears to be lower with pure tones (maximal loudness suppression with 5 ms durations) than with noise bursts, perhaps because pure tones are qualitatively distinct from the startle noise burst, and thus more easily detected and more salient. This same non-linear relationship between prestimulus salience and perceptual intensity has been demonstrated with prepulse effects on pain (Blumenthal et al., 2001), and indeed, with prepulse effects on startle magnitude (Blumenthal et al., 1996). Also, activation of both inhibitory and summation processes by prepulses in a prepulse-startle paradigm has been shown (Blumenthal & Levey, 1989; Wynn et al., 2000), with inhibition due to the onset transient aspects of the prepulse, and summation based on the steady-state body of the prepulse (increasing with increased duration, as in the PPIPSI finding of the present study).

Interpreting the effects of prepulse duration on PPIPSI in Experiment 2 is complicated by the relationship between prepulse duration and prepulse gap (time from prepulse offset to pulse onset): as prepulse duration was increased, the temporal gap separating prepulse and pulse diminished. However, some conclusions are possible: for example, the data demonstrate that *some* gap is necessary for the measurement of PPIPSI, at least under the present stimulus and experimental conditions. Furthermore, the effects of prepulse and gap duration on PPIPSI appear to be at least partially dissociable. For example, in Experiment 2, more PPIPSI was associated with a 70 ms gap compared to a 115 ms gap. In contrast, we previously reported the opposite “gap” pattern: greater PPIPSI with 115 ms gaps than with 55 ms gaps (Swerdlow et al., 2005). The key parametric difference behind these disparate findings is the duration of the prepulses: in Experiment 2, the shorter gap resulted from a longer prepulse duration (50 ms vs. 5 ms onset-to-offset), while in our previous studies (Swerdlow et al., 2005), prepulse duration was held constant (5 ms). These disparate findings are thus most easily reconciled by concluding that prepulse and gap duration contribute independently to PPIPSI, within particular dynamic temporal ranges (e.g. not at extreme values). A previous study (Blumenthal 1995) demonstrated the importance of prepulse but not gap duration in determining the amount of PPI, and used brief prepulse pairs to show that the effects of prepulse duration may be best accounted for by brief onset and offset transients. Similar mechanisms have not been tested with PPIPSI, but might be predicted based on the fact that some gap appears to be necessary for the measurement of PPIPSI.

It is possible that the effects of prepulse bandwidth and duration on loudness inhibition in Experiment 2 reflected differences in the perceived intensity of the prepulses. As a preliminary test of this hypothesis in 6 additional subjects, VAS ratings of the *prepulse stimuli* used in Experiment 2 revealed no significant effects of prepulse bandwidth ($F < 1$) or duration ($F(3,15) = 1.22$, ns) and no significant interaction. Prepulses were clearly rated as less intense than pulse stimuli (mean VAS for prepulses = 7.77 for noise and 11.03 for pure tone, vs. 33.45 for startle noise stimuli). Thus, significant effects of prepulse bandwidth and duration on %PPIPSI in Experiment 2, and the significant bandwidth $\times$ duration interaction for this measure, cannot be easily explained based on differences in the perceived intensity of the prepulses.

While prepulses inhibit both the motor response to, and loudness of, startling stimuli, it is likely that these two inhibitory processes reflect different neural mechanisms, and will inform us about different aspects of information processing. PPI of startle is a measure of sensorimotor gating, and the dependent measure is a motor response. PPI can be assessed in conditions in which test subjects are uninstructed, and which do not require the allocation of attentional resources. In contrast, PPIPSI reflects a subject's conscious assessment of a perceived event. No motor response is measured; in fact, PPIPSI is most reliably assessed using stimuli that produce submaximal motor responses (Swerdlow et al., 1999). Thus, the entire effector apparatus in the startle neural circuitry, which plays a crucial role in measures of PPI, does not participate in the assessment of PPIPSI (for a discussion of the contribution of "self-perceived startle" to PPIPSI, please see (Swerdlow et al., 1999)). One practical advantage of this independence of loudness assessment from startle is that meaningful VAS data is still obtained from startle "non-responders", as was the case in the present study.

Just as PPIPSI cannot be described as a measure of *sensorimotor gating*, it is also not a simple measure of *sensory gating*: the assessment of stimulus intensity requires mechanisms outside of the sensory apparatus. Both attentional mechanisms and higher cognitive and self-monitoring events must be engaged in the process of cross-modal matching, and differences in these mechanisms will likely impact the amount of, and parametric sensitivity of, PPIPSI. Subjects must attend to the compound stimulus, form an assessment of its intensity, and translate that assessment to a visual image of a distance on a line. We have previously reported that the process of attending to the compound stimulus does not alter the amount of startle or PPI to that stimulus (Talledo et al., 2004), so the impact of the attentional demands of PPIPSI appear to differ from those of instructed tasks associated with attentional modulation of PPI. Nonetheless, the complex path from stimulus presentation to response acquisition clearly captures processes beyond those associated with *sensory gating*, a moniker typically applied to the automatic inhibition of event-related potentials. Rather than attempt to label PPIPSI as a measure of a specific form of "gating", we have proposed that the simplest, most operational definition of this process is "prepulse inhibition of perceived stimulus intensity".

That PPIPSI likely reflects the interaction of complex sensory and cognitive processes does not diminish its potential importance in the study of information processing deficits in neuropsychiatric populations. Indeed, there is precious little evidence that "pure" measures of sensorimotor or sensory gating are directly informative about a host of important clinical issues, ranging from functional impairment to treatment responsivity. Nor does it suggest that a neural basis of PPIPSI cannot be studied experimentally. For example, Kedzior et al., (2006) report prepulse effects on theta oscillations during measures of PPI - activity that might encode precisely the types of complex processes that contribute to PPIPSI. Interestingly, prepulse effects on acoustically-evoked theta oscillations mimic in magnitude and temporal sensitivity the inhibition of perceived stimulus intensity assessed by PPIPSI. Because of its stability, reliability and simplicity, PPIPSI might have a range of applications, from biomarker to endophenotype - applications currently being explored for PPI and more technically complex gating measures (cf. Braff et al., 2001b; Braff & Freedman 2002). One might envision experiments in which the acquisition of VAS data outside of the laboratory via inexpensive, portable, PDA-based devices could offer advantages over laboratory-based collection of complex electrophysiological signals. Of course, any such utility for this measure is predicated on its systematic validation and parametric assessment, which is one aim of the present study.

In summary, prepulse effects on perceived stimulus intensity exhibit orderly though non-linear relationships to prepulse intensity and duration. Prepulse bandwidth impacts the time base of maximal perceptual inhibition. Patterns of prepulse effects on loudness and startle reflex magnitude continue to suggest that overlapping but non-identical neural mechanisms underlie these two forms of prestimulus-induced gating.

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Figure 1.

Effects of prepulse intensity on PPIPSI and PPI. (A) VAS ratings as a function of prepulse intensity. Inset shows intensity function for VAS scores for 100 and 105 dB(A) pulses. Asterisks indicate significantly lower than PA values. (B) %PPIPSI as a function of prepulse intensity. (C) Startle magnitude and (D) %PPI as a function of prepulse intensity for 13 startle “responders” in this session. Error bars: SEM.

Figure 2.

Effects of prepulse duration and bandwidth on PPIPSI and PPI. (A) VAS ratings as a function of prepulse duration and bandwidth. Inset shows intensity function for VAS scores for 100 and 105 dB(A) pulses. Asterisks indicate significantly lower than PA values; (‡) indicates significantly greater than PA for pure tone 120 ms prepulsees, $p < 0.005$. (B) %PPIPSI as a function of prepulse duration and bandwidth. Asterisks signify significantly greater than zero PPIPSI. For 50 ms duration prepulses, %PPIPSI with noise prepulses was significantly greater than with tones ($p < 0.003$). (C) Startle magnitude and (D) %PPI as a function of prepulse duration and bandwidth for 14 startle “responders” in this session. Error bars: SEM.