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A novel rat strain with enhanced sensitivity to the effects of dopamine agonists on startle gating

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Abstract

Background: Compared to outbred Sprague Dawley (SD) rats, inbred Brown Norway (BN) rats exhibit less prepulse inhibition of startle (PPI) at long prepulse intervals, and more PPI at short intervals. Sensitivity to dopaminergic drug effects on PPI differs substantially across strains, and is heritable within SD and other outbred strains. To further understand the heritability of PPI and its sensitivity to dopamine agonists, we assessed PPI and apomorphine sensitivity in SD, BN and F1 (SD × BN) rats.
Methods: PPI was measured in BN, SD and F1 rats under a variety of stimulus conditions, and after treatment with apomorphine.
Results: Findings confirmed significantly more PPI in BN compared to SD rats at short prepulse intervals, and significantly more PPI in SD compared to BN rats at long intervals. F1s were "supersensitive" to both the PPI-disruptive effects of apomorphine at longer intervals, and the PPI-enhancing effects of apomorphine at shorter intervals, compared to either parental strain.
Conclusion: Differences in sensorimotor gating between SD and BN rats are robust, time-locked and consistent across studies. Unlike patterns in other strains, heritability of PPI apomorphine sensitivity phenotypes in SD × BN F1s cannot be easily explained by simple additive effects.

Keywords: Apomorphine; Dopamine; Prepulse inhibition; Schizophrenia; Startle; Strain

1. Introduction

The ability of a weak lead stimulus to inhibit the motor response to a startling stimulus ("prepulse inhibition": PPI) is an operational measure of sensorimotor gating (Graham, 1975). Automatic, uninstructed PPI is deficient in several neuropsychiatric disorders, including schizophrenia (Braff et al., 1978; cf. Braff et al., 2001), and is being studied intensively as a means to understand the neurobiology and genetics of this disorder (cf. Braff and Freedman, 2002). However, low levels of PPI are not necessarily associated with pathology: normal humans exhibit a full range of PPI, from very low to very high levels. For example, normal men exhibit significantly more PPI than do normal women (Swerdlow et al., 1993). Even among normal men, some exhibit very low levels of PPI (Swerdlow et al., 2006b). Interestingly, clinically normal "low gating" and "high gating" men differ in their sensitivity to the regulation of PPI by both dopamine (DA) agonists (Swerdlow et al., 2003; Bitsios et al., 2005) and antagonists (Swerdlow et al., 2006b).

PPI levels also differ greatly across "normal" rat strains, as does the sensitivity of PPI to disruption by DA agonists (Swerdlow et al., 2004c). We reported that PPI in Brown Norway (BN) rats is significantly elevated at short prepulse intervals (10 ms) (Swerdlow et al., 2006b), and significantly reduced at long prepulse intervals (60–120 ms), compared to Sprague Dawley (SD) rats; the latter finding was previously described by Palmer et al. (2000) and Conti et al. (2001). SD rats are more sensitive to the PPI-disruptive effects of DA agonists, compared to other rat strains, and this differential sensitivity is inherited (Swerdlow et al., 2004a,b,c). One focus of our work has been to identify the neural basis for inherited differences in the sensitivity of PPI to DA agonists, and ultimately to define the neural circuit mechanisms by which genes regulate PPI deficits in neuropsychiatric disorders. While the neural circuit regulation of PPI has been studied more intensively in rats than in mice (cf. Swerdlow et al., 2001a), relatively less is understood about the heritability of PPI phenotypes in rats. To further study strain differences in, and the heritability of PPI phenotypes in rats, we

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assessed PPI and DA agonist sensitivity among SD and BN rats, and F1 rats from an SD × BN cross.

2. Methods

SD and BN rats (Harlan Labs; SD: San Diego, CA; BN: Indianapolis, IN) were the parental (F0) generation. SD, BN and F1 (SD × BN) rats were bred in-house and used in the present studies as adults. Based on the substantial difference in litter size across strains (mean litter size for SD vs. BN rats = 11.0 vs. 4.9), no attempt was made to balance litter sizes across strains via culling. In-house bred rats were weaned on post-natal day (pnd) 28 into same-sex cages of 2–3 and allowed to mature. Adult rats were maintained in same-sex rooms, on a reversed 12 h light/dark cycle. Testing and drug administration occurred in the dark phase. Rats were handled on pnd 50 to minimize stress during behavioral testing, and had food and water ad lib, except during testing. The final test sample of in-house bred rats consisted of SD (n = 33; 3 litters), F1 (n = 61; 8 litters: n = 39 from SD dams, n = 22 from BN dams) and BN (n = 44; 9 litters) rats. Each SD and BN litter was produced by a unique dam; the 8 F1 litters came from a total of 6 dams (two BN dams each produced 2 litters). SD (n = 73) and BN rats (n = 36) acquired from the vendor as adults were handled within 48 h of arrival, and were tested to determine whether rats bred in-house and at the supplier facility exhibited comparable startle phenotypes. All studies were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Animal Subjects Committee of the University of California San Diego (protocol #S01221).

Startle chambers (SR-LAB; San Diego Instruments) were housed in a sound-attenuated room (60 dB ambient noise) consisted of Plexiglas cylinders (8.7 cm internal diameter) resting on Plexiglas stands. Acoustic stimuli and background noise were presented by a speaker mounted 24 cm above the cylinder. Startle magnitude was detected and recorded as transduced cylinder movement via a piezoelectric device. Rats were exposed to a 'matching' startle session to balance drug groups based on average level of PPI.

Different test sessions were utilized, to assess different characteristics of startle and PPI (Table 1). To ultimately assign dose groups based on comparable levels of "baseline" PPI, rats were tested in a "matching session", consisting of 17 "P120" trials (40 ms noise bursts of 120 dB(A) intensity) and 3 "PP12" trials (20 ms noise bursts 12 dB over the 70 dB(A) background followed 100 ms later (onset to onset) by a P120). This session minimizes rat exposure to startle stimuli, while yielding PPI values that are stable and reliable for group assignment (Geyer and Swerdlow, 1998).

To assess strain differences in the sensitivity of startle inhibition to prepulse intensity, the "intensity session" included 128 trials of 9 trial types: (1) P120; (2) P120 preceded 100 ms by a 20 ms noise burst that was either 1, 2, 3, 4, 5, 10 or 15 dB above the 70 dB(A) background; and (3) "NOSTIM" trials, in which motor activity was assessed without stimulus presentation. To assess the relationship between startle magnitude and PPI across strains, the "low/high pulse session" included a total of 140 trials, consisting of both P120 and 105 dB(A) pulses (P105), P120 and P105 pulses preceded 100 ms by prepulses 3, 5 or 10 dB above the 70 dB(A) background, and NOSTIM trials. To assess the temporal properties of prepulse effects on startle, the "interval session" included 84 trials of 6 types: "P118" (40 ms noise bursts of 118 dB(A) intensity); P118 preceded 10, 20, 30, 60 or 120 ms by a prepulse (5 ms noise burst; this allows a return to background noise prior to startle stimulus onset for 10 and 20 ms prepulse intervals) 15 dB above the 70 dB(A) background; and NOSTIM trials. Intensity, high/low pulse and interval sessions began and ended with 3–4 pulse alone trials (P120 in the intensity and high/low pulse sessions, and P118 in the interval session). These initial and final trials were used to calculate reflex habituation.

Table 1
Testing sequence

Day	Sequence	Session	Drug	Prepulse intensity	Pulse intensity	Interstimulus interval
1	1	Matching	∅	82 dB	120 dB	100 ms
5	2	Intensity	∅	71–85 dB	120 dB	100 ms
12	3	Low/high	∅	73–80 dB	105 dB, 120 dB	100 ms
19	4	Interval	∅	85 dB	118 dB	10–120 ms
26	5	Interval	APO 0–0.5 mg/kg	85 dB	118 dB	10–120 ms
31	6	Interval	APO 0–0.5 mg/kg	85 dB	118 dB	10–120 ms
36	7	Interval	APO 0–0.5 mg/kg	85 dB	118 dB	10–120 ms

– All sound levels measured on the A Scale; all noise broad band (white noise).
– Background noise level 70 dB.
– Interstimulus interval is from onset of prepulse to onset of pulse.
– Sequence tests 5–7: within-subject dose–response study, using vehicle, 0.1 and 0.25 mg/kg APO.

Rats were tested sequentially, without drug administration, in the matching, intensity, low/high pulse and interval sessions, with 5–7 days between tests beginning 1 week after arrival or on d57 for in-house bred rats (Table 1). They were then tested three additional times in the interval session, in each case immediately after treatment with vehicle (saline/0.1% ascorbate), 0.1 or 0.25 mg/kg APO (sc), with dose order balanced within- and across rat strains and sexes. Test days in this APO dose–response study were 4–5 days apart. The interval session, in this precise form (including P118 stimuli) has been used in our laboratory to study the effects of DA agonists and antagonists on PPI in "low vs. high gating" humans (Swerdlow et al., 2004a, 2006a,b).

Startle variables included startle magnitude on pulse alone trials, habituation (percent change in startle from the initial to the final 3 pulse alone trials), %PPI (100 − [(startle amplitude on prepulse trials / startle amplitude on P-ALONE trials) × 100]) and NOSTIM levels. Significant differences in %PPI were examined to determine the relative contribution to this difference of changes in startle magnitude on pulse alone vs. prepulse + pulse trials. All variables were analyzed by one-factor (habituation) or repeated measures ANOVA, with trial type and drug dose as within-subject factors, and strain as a between-subject factor. Sex differences in PPI were reported for the interval session without a drug challenge, but for simplicity, no interaction effects of sex are reported in the APO dose–response study; qualitative descriptions are provided, confirming a replication of

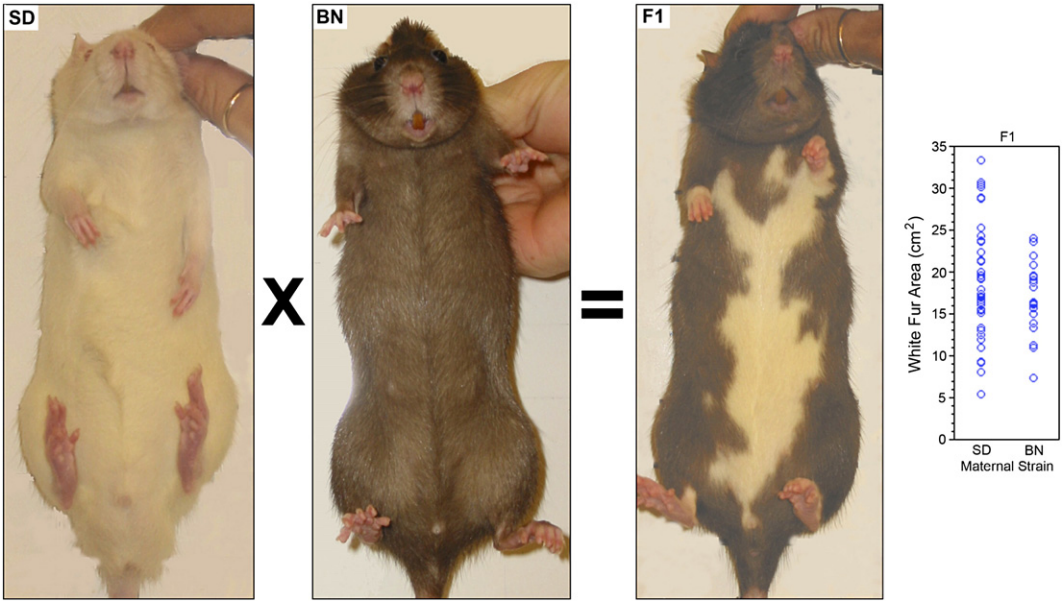

Fig. 1. Pigmentation patterns in albino SD, solid brown BN, and "patched" F1, showing typical distribution of unpigmented fur on the ventrum of F1s. Total area of white fur in F1s is shown at right, divided by maternal strain. In a minority of BN rats (14.6%), a single spot of white fur (<1 cm^2) could be detected on the ventrum. In previous reported crosses of albino SD and hooded Long Evans rats, the amount of pigmentation in offspring has been found to correlate significantly with PPI APO sensitivity and D2-linked G-protein function (Swerdlow et al., 2004c, 2006a). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

all sex-specific patterns that had been observed in the drug-free interval test. In addition, ANCOVAs performed for the intensity session, high/low pulse session and interval session, confirmed no significant impact of body weight on PPI or PPI sex differences (no significant main effects of weight or sex × weight interactions). The ability of APO to disrupt PPI was compared using a measure of "APO effect", calculated as "[%PPI after vehicle] minus [%PPI after APO]", as described previously (Swerdlow et al., 2004c). Comparisons of in-house bred vs. purchased F0 strains revealed no significant differences in any PPI measures, and thus in-house bred and purchased rats were combined in the final strain analyses. In a small number of cases (<1%), startle magnitude was too low (<10 units compared to group means of approximately 200 units) to reliably calculate % PPI, and these rats were excluded from the analyses. Unless indicated otherwise, alpha was 0.05.

3. Results

3.1. General description of F1 strain

In contrast to the albino (SD) or fully pigmented (BN) parental strains, F1 rats exhibited a patched pigment distribution, with white fur across much of the ventrum, and pigmented fur across much of the rest of the body (Fig. 1). Subjectively, BN rats were more easily handled, compared to SD rats, with F1s exhibiting an intermediate phenotype. Litter sizes and sex distributions of the 3 strains are seen in Table 2. Litter sizes were greatest in SD rats, followed by F1 and then BN rats ($F=6.45$, df 2, 15, $p<0.01$; SD vs. BN: $p<0.01$; F1 vs. BN, $p<0.015$). Litter sizes in F1 rats corresponded to maternal strain (litter sizes from maternal SD=12–14; litter sizes from maternal BN=3–8).

3.2. Startle phenotypes

Results are first summarized for each test session below, followed by a detailed description of the statistical support for each summary:

3.2.1. Intensity session

PPI for SD, BN and F1 male and female rats, using prepulse intervals of 100 ms and prepulses of 1–15 dB over the 70 dB(A) background is seen in Fig. 2. Greater PPI in SD compared to BN rats was evident for all prepulse intensities above 1 dB. Greater PPI in male than female rats was also evident in all strains, though it was most evident in F1s. PPI in F1 males was comparable to the SD parental strain, while F1 females exhibited an intermediate phenotype. As previously reported (Palmer et al., 2000), startle magnitude was significantly greater in SD vs. BN rats (Fig. 2, inset), and startle magnitude in F1s resembled the BN phenotype, in contrast to patterns exhibited with PPI. Habituation in both SD and F1 rats significantly exceeded that in BN rats.

ANOVA of %PPI revealed significant effects of strain ($F=47.37$, df 2, 239), sex ($F=31.55$, df 1, 239), and intensity ($F=323.69$, df 6, 1434) (all $ps<0.0001$), and significant interactions of strain × sex ($F=4.06$, df 2, 239, $p<0.02$), intensity × strain

Table 2
Litters bred in-house for the present studies

Paternal strain	Maternal strain	Number of litters	Litter size (mean (range))	Male: female
SD	SD	3	11.0 (9–14)	15:18
BN	SD	3	13.0 (12–14)	20:19
SD	BN	5	4.4 (3–8)	7:15
BN	BN	9	4.9 (2–8)	26:18

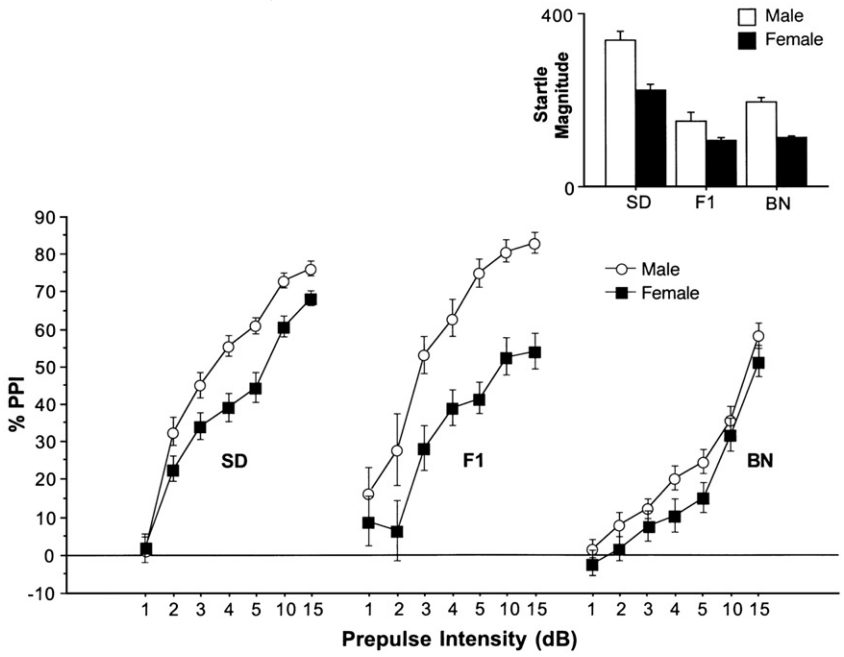

Fig. 2. Strain and sex differences in PPI among SD, F1 and BN rats, across a range of prepulse intensities. Greater PPI in SD vs. BN rats was evident for all prepulse intensities above 1 dB. Greater PPI in males than in females was evident to some degree in all strains, most notably in F1s, and least so in BNs. PPI in F1 males was comparable to the SD parental strain, while F1 females exhibited an intermediate phenotype. Inset: startle magnitude was significantly greater in SD vs. BN rats, and startle magnitude in F1s resembled the BN phenotype.

($F=12.89$, df 12, 1434, $p<0.0001$) and intensity × sex ($F=4.64$, df 6, 1434, $p=0.0001$). Post-hoc comparisons revealed significantly less PPI in BN than SD ($p<0.0001$) and F1 rats ($p<0.0001$); this was also evident in separate comparisons in male rats and in female rats. Sex differences in PPI (male > female) were evident in SD ($p<0.003$) and F1 rats ($p<0.0001$), but only reached trend levels in BN rats ($p<0.09$), perhaps due to a floor effect.

Because both litter size and PPI were greater in SD than BN rats, we attempted to assess the potential relationship between these variables. While litter sizes in these parental strains were either uniformly large (SD) or small (BN), litter sizes in F1 rats were divided based on the maternal strain, and ranged from very small ($n=3$) to very large ($n=14$). Importantly, ANOVA of % PPI in F1 rats revealed no significant effect of litter size ($F<1$) or of maternal strain ($F<1$).

Extreme differences in startle magnitude between groups can contribute to differences in %PPI, based on floor or ceiling effects. Startle magnitude was significantly greater in SD than in F1 and BN rats (main effect of strain: $F=57.72$, df 2, 239, $p<0.0001$; SD vs. F1: $p<0.0001$; SD vs. BN: $p<0.0001$). ANOVA also revealed a significant effect of sex (male > female: $F=36.36$, df 1, 239, $p<0.0001$), but no significant sex × strain interaction. Median splits were used to create groups with intermediate and balanced startle magnitude levels, using the lower 50% from the SD group, and the upper 50% from the F1 and BN groups. Among these rats with comparable startle magnitude (effect of strain: $F<1$), there remained significant strain differences in %PPI ($F=34.61$, df 2, 116, $p<0.0001$), with a pattern indistinguishable from that of the whole sample. To prospectively address the relationship of the observed strain differences in startle magnitude to those in %PPI, a separate test session was used, with low and high startle pulse intensities.

Reflex habituation in both SD and F1 rats significantly exceeded that in BN rats ($p<0.0001$, both comparisons).

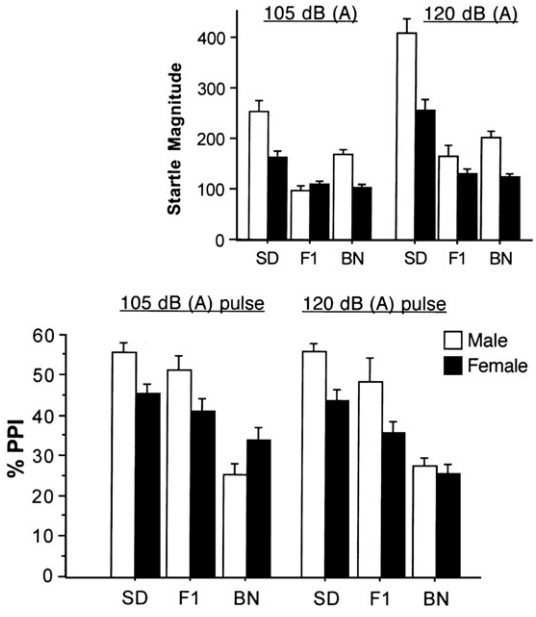

Fig. 3. Strain and sex differences in PPI (averaged across prepulse intensities) are independent of levels of startle magnitude. Note similar profiles of %PPI elicited with 105 dB(A) and 120 dB(A) pulses. Inset: startle magnitude on pulse alone trials. Note that startle elicited by 105 dB(A) pulses in SD rats (far left) does not differ significantly from startle elicited by 120 dB(A) pulses in BN rats (far right). Despite this, graph below shows that under these conditions of comparable startle magnitude, SD rats exhibited nearly twice as much PPI, compared to BN rats ($p<0.0001$).

Percent habituation (mean (SEM)) across the 3 strains was 60.88 (2.34)% for SD, 66.00 (4.88)% for F1 and 26.7 (6.25)% for BN rats.

3.2.2. Low/high pulse session

Fig. 3 shows PPI for SD, BN and F1 male and female rats, using 105 dB(A) and 120 dB(A) pulses, prepulse intervals of 100 ms and prepulses of 3, 5 and 10 dB over the 70 dB(A) background. This session was used to assess the potential contribution of strain differences in startle magnitude on the "low vs. high gating" phenotypes. Startle magnitude in SD rats with 105 dB(A) pulses was most comparable to that of BN rats with 120 dB(A) pulses (see Fig. 4, inset, bars at far left vs. far right). Despite relatively "matched" levels of startle magnitude, PPI on these trials was significantly greater in SD vs. BN rats. Other patterns observed in the "intensity session" were also evident in the "low/high pulse session", including greater PPI in males than in females, an intermediate PPI phenotype in F1 females (compared to SD and BN females), and lower startle magnitude in BN and F1 rats, compared to SD rats. Strain differences in habituation were also detected (F1 > SD >> BN).

ANOVA of %PPI revealed significant effects of strain ($F=36.17$, df 2, 231, $p<0.0001$), sex ($F=7.84$, df 1, 231, $p<0.007$) and prepulse intensity ($F=367.04$, df 2, 462; $p<0.0001$), and significant interactions of strain × sex ($F=4.49$, df 2, 231, $p<0.015$) and prepulse intensity × sex ($F=4.77$, df 1, 231, $p<0.01$). Importantly, there were no significant effects of pulse intensity ($F<1$) or interactions of pulse intensity × strain ($F<1$). Post-hoc comparisons revealed the same general relationships observed in the intensity session: significantly less PPI in BN than SD ($p<0.0001$) and F1 rats ($p<0.0001$); this was also evident in separate comparisons in male rats and in female rats. Also as with the intensity session, sex differences in PPI (male > female) were evident in SD ($p<0.005$) and F1 rats ($p<0.003$), but not in BN rats.

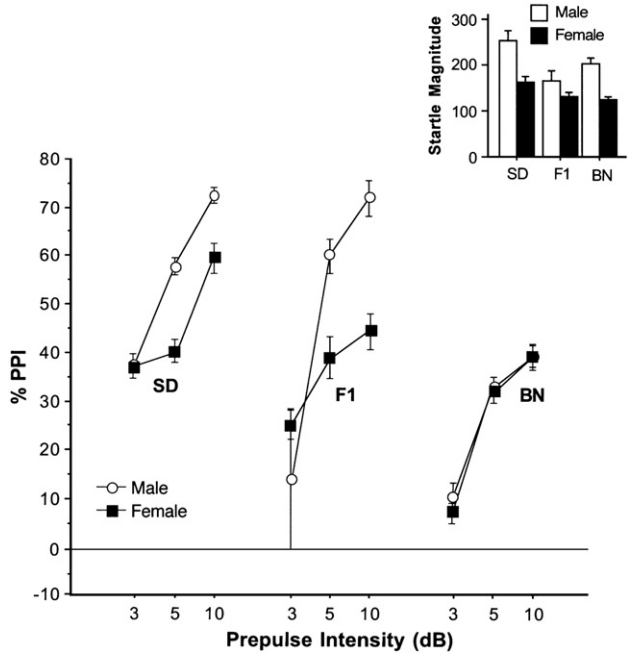

Fig. 4. %PPI in the low/high pulse session, under conditions that generate roughly comparable startle magnitude in SD rats (105 dB(A) pulses), and F1 and BN rats (120 dB(A) pulses). Despite the fact that ANOVA of startle magnitude (inset) revealed no significant effect of strain, ANOVA of PPI (main graph) confirmed the phenotypic patterns for male (SD = F1 > F1 > BN) rats.

ANOVA of startle magnitude revealed the expected pattern of SD > F1 and SD > BN rats (main effect of strain: $F=50.15$, df 2, 231, $p<0.0001$; SD vs. F1: $p<0.0001$; SD vs. BN: $p<0.0001$) and effects of sex (male > female: $F=26.21$, df 1, 231, $p<0.0001$) and pulse intensity ($F=123.20$, df 1, 231, $p<0.0001$). There were significant interactions of strain × sex ($F=5.62$, df 2,231, $p<0.005$), pulse intensity × strain ($F=28.64$, df 2, 231, $p<0.0001$) and pulse intensity × sex ($F=11.61$, df 1, 231, $p<0.001$).

Most importantly, when startle magnitude on 105 dB(A) pulses in SD rats was combined in an analysis with startle magnitude on 120 dB(A) pulses in F1 and BN rats, ANOVA revealed no significant main effect of strain on startle magnitude. Using these data, ANOVA of %PPI confirmed key patterns detected previously: significant main effects of strain ($p<0.0001$), with post-hoc verification of SD > BN and F1 > BN levels of %PPI (p's <0.0001) (Fig. 4). Thus, significant strain differences in PPI were evident using startle stimuli that yielded comparable levels of startle magnitude across the three strains.

Reflex habituation in both SD and F1 rats significantly exceeded that in BN rats ($p<0.001$ and $p<0.0001$, respectively). Habituation in F1 rats also exceeded that in SD rats ($p<0.004$). Percent habituation (mean (SEM)) across the 3 strains was 55.30 (3.84)% for SD, 74.13 (3.14)% for F1 and 35.63 (5.44)% for BN rats.

3.2.3. Interval session, no drug administration

PPI for SD, F1 and BN male and female rats using 10–120 ms prepulse intervals is seen in Fig. 5. Interval-specific PPI differences between SD and BN rats were evident: compared to SD rats, BN rats exhibited significantly more PPI at 10 ms prepulse intervals, and significantly less PPI at longer prepulse intervals. These phenotypic differences were evident in both male and female rats. The temporal pattern of PPI in F1 rats most closely resembled those of the SD parental strain, though the amount of PPI in F1 females was again intermediate between the parental SD and BN strains. Across all strains, male > female PPI was evident at longer prepulse intervals; this pattern was also evident in BN rats at short intervals, while in SD and F1 rats, the opposite pattern (female > male PPI) was detected at short intervals. As in the previous test sessions, differences in startle magnitude were detected (SD >> BN), and again in contrast to PPI, the startle magnitude phenotype in F1 rats resembled that of BN rats. Also as in previous sessions, reflex habituation in SD and F1 rats exceeded that in BN rats.

ANOVA of %PPI revealed significant main effects of strain ($F=22.50$, df 2, 238, $p<0.0001$) and interval ($F=126.23$, df 4, 952, $p<0.0001$), and significant interactions of strain × sex ($F=3.19$, df 2, 238, $p<0.05$), strain × interval ($F=16.88$, df 8, 952, $p<0.0001$), sex × interval ($F=9.45$, df 4, 952, $p<0.0001$) and strain × sex × interval ($F=4.24$, df 8, 952, $p<0.0001$).

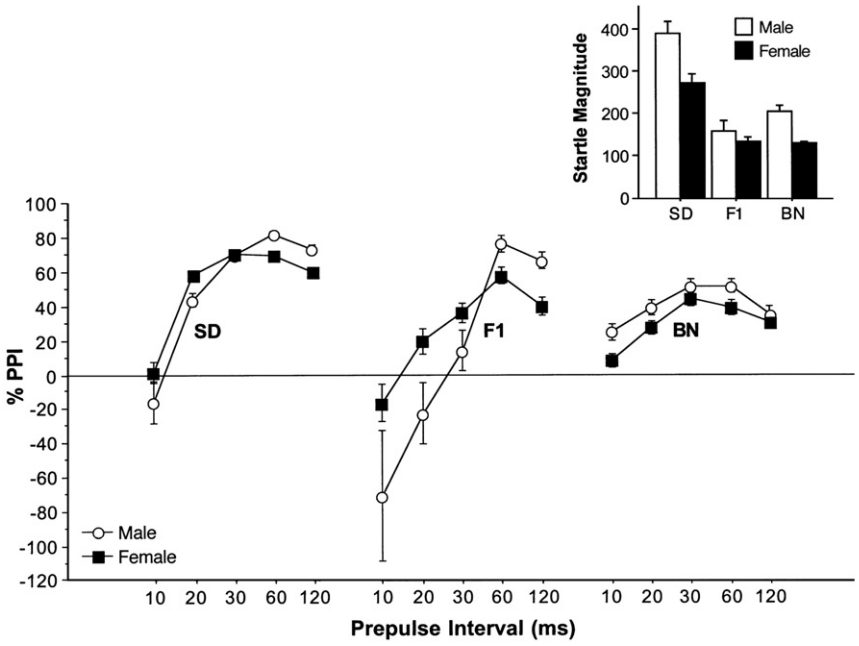

Fig. 5. Strain and sex differences in PPI among SD, F1 and BN rats, across a range of prepulse intervals. Compared to SD rats, BN rats exhibited more PPI at 10 ms prepulse intervals, and less PPI at longer prepulse intervals. The temporal pattern of PPI in F1 rats most closely resembled the SD parental strain, though the amount of PPI in F1 females was intermediate between SD and BN strains. Male > female PPI was evident at longer prepulse intervals for all strains; this pattern was also evident in BN rats at short intervals, while in SD and F1 rats, the opposite pattern (female > male PPI) was detected at short intervals. Inset: startle magnitude shows the expected strain (SD > > F1, BN) and sex differences. As described in the text, one "outlier" rat (%PPI < − 1900 at 20 ms interval) was removed from the analyses, though this did not alter any of the significant statistical outcomes.

Elimination of one "outlier" rat (%PPI < − 1900 at 20 ms interval) yielded an identical pattern of statistics (with larger F values reflecting the reduced variance), except for the interaction of strain × sex, which no longer achieved statistical significance ($F = 1.84$, df 2, 237, ns). Post-hoc comparisons revealed significantly greater PPI in BN rats than SD ($p < 0.015$) and F1 ($p < 0.0001$) rats at 10 ms prepulse intervals, SD > F1s and BN > F1s for 20–30 ms prepulse intervals ($ps < 0.0001$), and SD > BN PPI at prepulse intervals ≥ 20 ms ($ps < 0.0001$). In BN rats, male > female PPI was evident across the full temporal range (main effect of sex: $p < 0.015$, sex × interval interaction ns); for SD and particularly F1 rats, sex differences in PPI were interval-dependent: female > male PPI was evident at short (<30 ms: $p < 0.005$) prepulse intervals, and male > female PPI was evident at 60–120 ms intervals ($p < 0.0001$).

ANOVA of startle magnitude on pulse alone trials confirmed the identical pattern detected in the previous test sessions: greater startle magnitude in SD than BN ($p < 0.0001$) or F1 rats ($p < 0.0001$), and in males compared to females ($p < 0.0001$).

Reflex habituation in both SD and F1 rats significantly exceeded that in BN rats ($p < 0.0001$, both comparisons). Percent habituation (mean (SEM)) across the 3 strains was 60.56 (2.66)% for SD rats, 72.11 (3.52)% for F1 rats and 19.15 (7.22)% for BN rats.

3.2.4. Interval session, APO dose–response study

PPI in SD, F1 and BN rats after treatment with vehicle, 0.1 or 0.25 mg/kg APO sc is seen in Fig. 6. APO caused a significant dose-dependent reduction in long interval PPI (60–120 ms prepulse intervals) in SD rats, as expected. Also consistent with previous findings (Swerdlow et al., 2004c), the dose-dependent APO-induced reduction in long interval PPI in BN rats was smaller in comparison to that in SD rats, potentially due to a "floor effect". F1 rats exhibited the most robust APO-induced disruption of PPI, with 0.1 mg/kg APO reducing long interval PPI significantly more in these rats than in either of the parental strains. In SD rats, APO did not significantly increase PPI at short prepulse intervals (10–20 ms), though this effect was detected in BN rats. As with the effects of APO at long intervals, those at short intervals were significantly greater in F1 rats than in either parental strain.

Startle magnitude on pulse alone trials (Fig. 6, inset) was reduced by APO in SD and F1 rats. As previously reported, APO effects on startle magnitude could be clearly dissociated from those on PPI. For example, 0.1 mg/kg APO caused no change in startle magnitude in F1 rats, despite robust changes in PPI. Reflex habituation was relatively unaffected by APO; after vehicle treatment, habituation in SD and F1 rats significantly exceeded that in BN rats, as observed in all other test sessions.

ANOVA of %PPI revealed significant effects of APO dose ($F = 4.77$, df 2, 350, $p < 0.01$) and prepulse interval ($F = 127.99$, df 4, 700, $p < 0.0001$), and significant interactions of dose × strain ($F = 3.29$, df 4, 350, $p < 0.012$), strain × interval ($F = 15.96$, df 8, 700, $p < 0.0001$), dose × interval ($F = 33.94$, df 8, 1400, $p < 0.0001$) and dose × strain × interval ($F = 7.07$, df 16, 1400, $p < 0.0001$). To simplify and understand these 2- and 3-way interactions, an "APO PPI effect" variable was calculated, based on the difference in PPI under vehicle minus APO conditions, for each dose of APO. For the "threshold" dose of 0.1 mg/kg APO, ANOVA revealed a greater APO impact at 10–20 ms

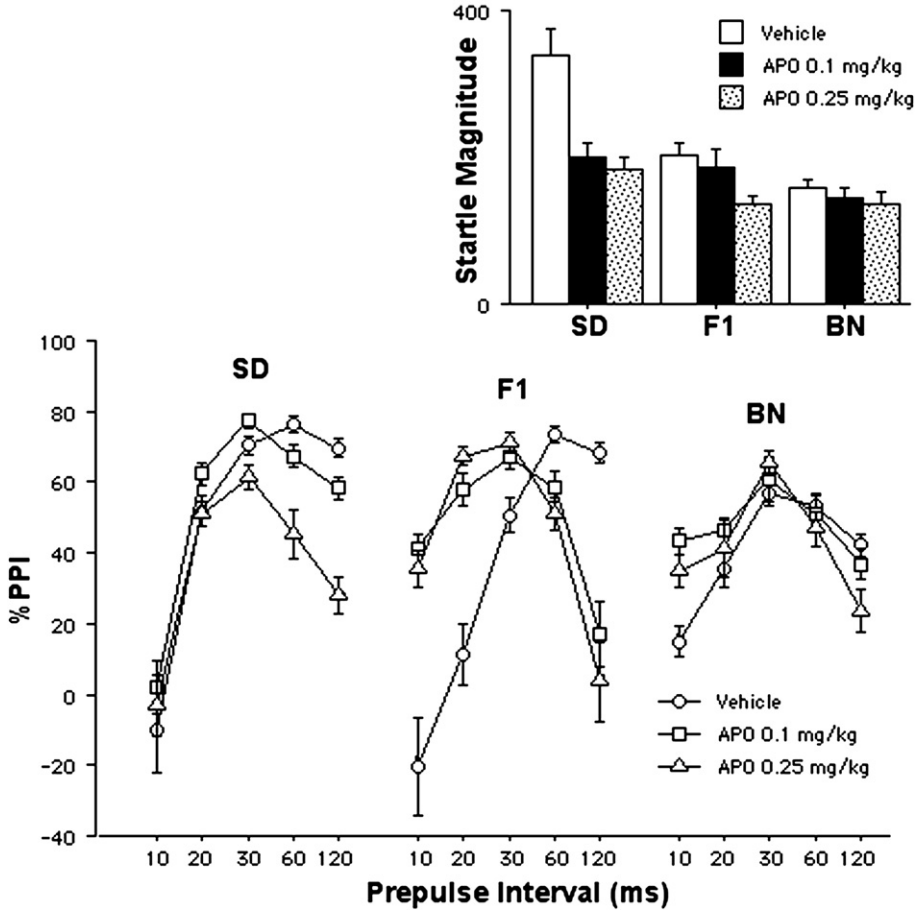

Fig. 6. Effects of APO on PPI across 10–120 ms prepulse intervals in male and female rats. APO suppressed long interval PPI (60–120 ms prepulse intervals) in SD rats; this effect in BN rats was smaller, possibly due to a "floor effect". F1 rats exhibited the most robust APO-induced disruption of PPI, with 0.1 mg/kg APO reducing long interval PPI significantly more in these rats than in either of the parental strains. At short prepulse intervals, APO did not significantly increase PPI in SD rats, but did so in BN rats. Here again, the effects of APO were significantly greater in F1 rats than in either parental strain. Inset: startle magnitude was generally reduced by APO, but this effect showed no clear relationship with changes in PPI (e.g. no significant APO effect on startle magnitude in either F1 or BN males, who showed substantial differences in APO effects in both short- and long interval PPI).

intervals ($p<0.002$–0.0002) in F1 vs. SD rats (increasing PPI), at 10 ms prepulse intervals ($p<0.045$) in F1 than BN rats (increasing PPI), and at 60–120 ms in F1 vs. either SD ($p<0.0001$) or BN rats ($p<0.0001$) (decreasing PPI). A very similar pattern was evident for the higher APO dose: a greater APO impact at 10–30 ms intervals ($p<0.004$–0.0001) in F1 vs. SD rats (increasing PPI), at 10–20 ms prepulse intervals ($p<0.04$–0.0001) in F1 than BN rats (increasing PPI), at 60 ms for SD vs. BN rats ($p<0.004$, decreasing PPI), and at 120 ms in F1 vs. either SD ($p<0.05$) or BN rats ($p<0.0002$) (decreasing PPI). In each strain, males and females exhibited sex-specific PPI patterns described above in the drug-free interval session. Males and females also exhibited qualitatively similar temporal response patterns to APO, with males exhibiting quantitatively greater APO sensitivity in SD and BN rats, both in terms of the magnitude of the APO effect, and in terms of the temporal period over which those APO effects were manifested (e.g. greater APO effects of PPI over 30–120 ms intervals in male vs. female SD rats, and greater APO effects on PPI over 10–30 ms intervals in male vs. female F1s).

ANOVA of startle magnitude on pulse alone trials revealed significant main effects of strain ($F=9.48$, df 2, 175, $p<0.0001$) and APO dose ($F=23.43$, df 2, 359, $p<0.0001$), and a significant interaction of strain × dose ($F=7.62$, df 4, 350, $p<0.0001$). Post-hoc comparisons revealed significant APO-suppression of startle magnitude in SD ($p<0.0001$) and F1 rats ($p<0.005$) but not BN rats; only those effects in F1 rats were dose-dependent.

Percent reflex habituation revealed patterns similar to those in other test sessions: after vehicle treatment, habituation in SD and F1 rats significantly exceeded that in BN rats ($p<0.0001$, both comparisons). Percent habituation (mean (SEM)) across the 3 strains was 53.65 (3.56)% for SD rats, 63.01 (5.54)% for F1 rats and 18.49 (9.95)% for BN rats.

Distributions of APO sensitivity at 10 and 120 ms prepulse intervals, across SD, F1 and BN strains (Fig. 7A) did not suggest that F1 rats segregate into subpopulations with different PPI APO sensitivity at either prepulse interval. Interestingly, in F1 rats, the APO-induced increase in PPI at 10 ms prepulse interval did not correlate with the APO-induced decrease in PPI

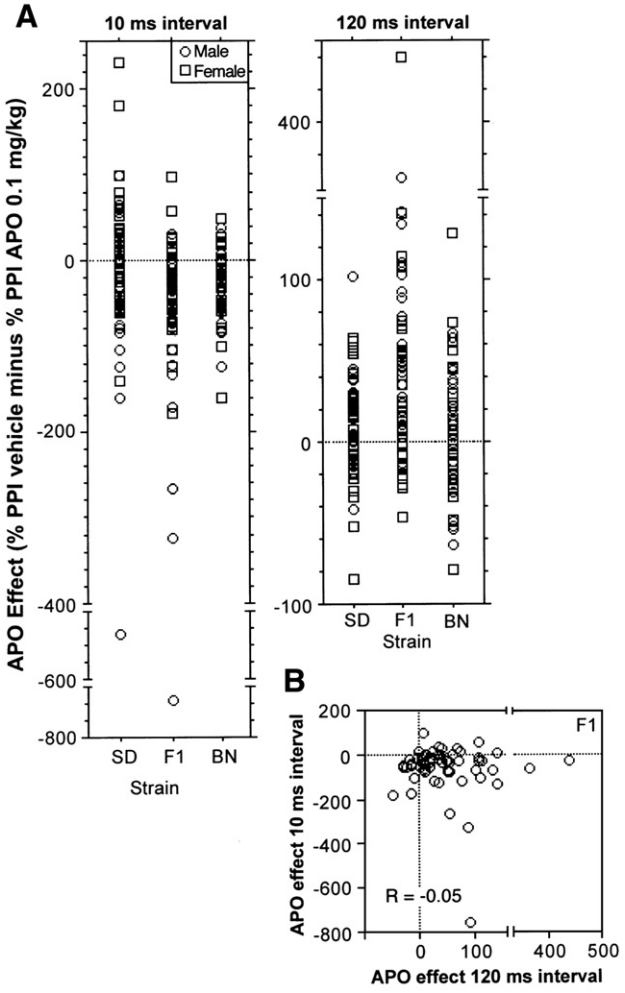

Fig. 7. A. Distributional patterns of APO sensitivity in SD, F1 and BN rats for 10 ms (left) and 120 ms (right) prepulse intervals. *Y*-axis "APO effect" is equal to the difference between vehicle and APO levels of PPI for individual rats. A negative value (seen predominantly at 10 ms intervals) reflects an APO-induced increase in PPI, while a positive value (seen predominantly at 120 ms prepulse intervals) reflects an APO-induced decrease in PPI. The distributional properties of F1 rats do not suggest any clear segregation into subpopulations with distinct phenotypes. B. Regression plot of APO effect at 10 ms intervals (*Y*-axis) and 120 ms intervals (*X*-axis) in F1 rats. Among the 3 strains, APO sensitivity of F1 rats was greatest at both 10 and 120 ms prepulse intervals, yet for any single F1 rat, these two phenotypes were independent.

at 120 ms prepulse intervals ($R=0.02$; Fig. 7B), suggesting that these effects are mediated by separable DAergic substrates, both of which appear to be "more sensitive" in F1 rats. Finally, a single variable representing the sensitivity to 0.1 mg/kg APO was calculated for each F1 rat at each prepulse interval, based on the absolute value of the APO PPI effect (PPI: vehicle minus APO). This value of APO sensitivity was weakly and inversely related to each rat's body surface area of white fur ($R=-0.29$, $p<0.05$).

In an attempt to examine potential epigenetic contributions to the main phenotypes in this study, among F1 rats, we found no significant main or interaction effect of maternal strain on PPI or APO sensitivity. We also did not detect any significant correlations between litter size and either PPI or APO sensitivity. Possible litter effects were assessed in each strain for all sessions (9 sets of comparisons), with no effects reaching the corrected alpha of 0.0056 (one analysis – PPI across the 9 BN litters in the intensity session – reached $p<0.025$; no other comparison for any strain in any test session reached $p<0.2$).

4. Discussion

In rodents, PPI has strong genetic determinants (cf. Geyer et al., 2002; Willott et al., 2003; Francis et al., 2003). Francis et al. (2003) provided an elegant demonstration that the PPI phenotype in specific mouse strains is determined by the genotype of the mouse embryo, and not by the genotype of either the maternal uterine or rearing environments. Tucci et al. (2006) provided complementary information supporting the importance of genetic vs. environmental influences on PPI. We previously reported that selective breeding of outbred SD and hooded LE strains (that do not differ in basal PPI levels) produced F1 and backcrossed N2 strains that exhibited basal levels of PPI comparable to the parental strains, but levels of PPI APO and AMPH sensitivity that were intermediate between the parental strains (Swerdlow et al., 2003, 2004a,b). The observed strain differences could not be explained on the basis of differential regional brain levels of APO (Swerdlow et al., 2002) or on strain differences in maternal behavior (Swerdlow et al., 2004a). These findings led us to suggest that PPI sensitivity to DAergic activation is a heritable phenotype expressed in an additive pattern across generations (e.g. crossing a high sensitivity strain with a low sensitivity strain produced a strain with intermediate sensitivity). Others have also identified heritable patterns of PPI sensitivity to DAergic activation in rats (Ellenbroek et al., 1995).

However, the present findings suggest that patterns of inheritance for PPI, and particularly for PPI APO sensitivity, do not follow such a simple, additive pattern. For example, in terms of sensitivity to prepulse *intensities*, under the current test conditions, SD and BN rats exhibit half-maximal inhibition (HMI) with prepulses that are 3 and 10 dB over background, respectively. As a group, F1s expressed an intensity-dependent PPI phenotype comparable to SD rats, with an HMI value of 3 dB; for maximal inhibition with 15 dB over background prepulses, F1 males exhibited levels comparable to SD males, while F1 females exhibited levels comparable to BN females. The failure to detect a simple additive pattern was even more evident in the phenotype of PPI APO sensitivity, which was significantly greater in F1 rats than it was in either parental strain, both for the APO-induced increase in short interval PPI, and for the APO-induced decrease in long interval PPI.

For other startle phenotypes, F1 rats generally exhibited that of one or the other parental strain, rather than intermediate levels. For example, startle magnitude in F1 rats was comparable to that of BN rats, and significantly lower than that of SD rats. In contrast, reflex habituation (calculated as a percent value, based on the observed differences in startle magnitude) in F1 rats was generally comparable to that of SD rats (exceeding SD values in one comparison), and like SD rats,

F1 habituation significantly exceeded habituation in BN rats in all comparisons.

The present studies left untested many possible explanations that might make the findings less interesting. Do the present results simply reflect strain differences in hearing threshold? Not likely: BN rats exhibit *more* PPI than SD and F1 rats to 15 dB prepulses with 10 ms intervals, and *less* PPI than SD and F1 rats to the same intensity (15 dB) prepulses with 120 ms intervals. This pattern cannot easily be explained on the basis of elevated hearing thresholds in BN rats. While hearing thresholds of BN rats have not, to our knowledge, been directly compared to SD or SD × BN F1 rats, their hearing thresholds could not account for reduced PPI relative to Wistar-derived rats (Palmer et al., 2000). Do the results reflect strain differences that are modality-specific, and thus less generally applicable to information processing mechanisms? While we are presently examining this possibility, this did not explain reduced long interval PPI in BN rats compared to Wistar-derived inbred rats (Palmer et al., 2000). Do the results reflect generalized strain differences in the ability of drugs to disrupt PPI, rather than neurochemically specific mechanisms? It appears not: in ongoing studies, we have determined that enhanced PPI sensitivity in F1s is specific to DA agonists, and is not evident in response to the NMDA antagonist, phencyclidine. We previously detected such neurochemical specificity in other heritable strain differences in PPI drug sensitivity (Swerdlow et al., 2004c).

In human brain disorders, the phenotypes related to reduced gating are not inherited in a simple additive pattern. In the case of schizophrenia, this has been demonstrated with event-related potential measures of sensory gating, perhaps even more convincingly than with PPI. With these measures, clinically unaffected parents – including perhaps one with, and one without, an intermediate deficient gating phenotype (Myles-Worsley, 2002; Cadenhead et al., 2000; Kumari et al., 2005) – produce affected F1s (probands) who express fully deficient gating. The non-additive PPI inheritance in the present study is most evident in the finding that PPI APO sensitivity – both the enhancement of short interval PPI and the disruption of long interval PPI – was significantly *greater* in F1 rats than in *either* parental strain. We are not proposing that these strains model the inheritance of gating deficits in schizophrenia, but only that F1s clearly expressed a "hidden" vulnerability to the impact of DA receptor stimulation on PPI (both at short and long prepulse intervals), that could not be predicted by either parental strain. The lowest dose of APO (0.1 mg/kg) caused extreme changes in F1 gating properties, producing a PPI temporal function that "overshot" the flat temporal function of BN rats to reach a full inversion of the SD temporal profile, with short interval PPI levels exceeding those at long intervals. Theoretically, in F1s, a small amount of DAergic activation caused information to be "super" protected in the immediate aftermath of the prepulse (10–30 ms), but left this information especially vulnerable to interruption 60–120 ms after the prepulse. At a conceptual level, such a pattern might accompany a change not only in the *amount* – but also in the *content* – of information that is protected for orderly, hierarchical processing, vs. left vulnerable to disruption by competing intero- and exteroceptive events (Swerdlow, 1996; Swerdlow et al., 2004a).

That such a distinct phenotype can emerge in one generation suggests a more complex pattern of heritability than we had proposed previously for PPI APO sensitivity in SD × LE crosses (Swerdlow et al., 2004a). Rather than being intermediate between parental strains, the F1 PPI phenotype in the presence of DAergic stimulation appears as an exaggerated version of the BN phenotype: both an exaggerated elevation of short interval PPI, and an exaggerated reduction in long interval PPI, the magnitudes of which are not correlated within individual rats. That these two processes do not travel together across generations suggest that they may be under separate neurobiological control. Our previous studies suggest that in SD and pigmented LE rats, the effects of APO on long interval inhibition are most potently regulated by D2 substrates, while APO effects on short interval potentiation are most potently regulated by D1 mechanisms (Swerdlow et al., 2004a).

Compared to studies in rats, studies of the genetics of basal PPI in mice are substantially more advanced (cf. Geyer et al., 2002), based on the greater understanding of the mouse genome, the technical ability to manipulate genes in the service of developing mutant mouse strains, and the more favorable economics associated with high throughput screening in mouse strains. Thus, for the purposes of mapping genes associated with basal levels of PPI, it is clear that mouse models offer great advantages over studies in rats. This species advantage is particularly evident over outbred rat strains, for which relatively few genomic markers exist (but see http://rgd.mcw.edu/strains/). That being said, our current understanding of the genetics of basal PPI reflects findings in both rats and humans, in addition to mice. In general, these include three types of reports. First, PPI deficits in specific genetic disorders, such as Huntington's Disease (HD) (Swerdlow et al., 1995; Valls-Sole et al., 2004) and 22q11 deletion syndrome (Sobin et al., 2005) suggest that the genes affected in both of these disorders modify brain circuitry that regulates PPI. In these instances, mouse models with homologous genetic defects also exhibit PPI deficits (Carter et al., 1999; Paylor et al., 2006; Van Raamsdonk et al., 2005). Second, quantitative trait loci (QTLs) have been identified, either through interval mapping in inbred rat strains (Palmer et al., 2003; Vendruscolo et al., 2006) or recombinant congenic mouse strains (Joober et al., 2002), or through the use of chromosome substitution strains in mice (Petryshen et al., 2005). Third, reverse genetic approaches in mice have identified a long list of genes (and molecules that they encode) that are associated with a reduction in PPI when inactivated via constitutive or conditional knock out techniques (cf. Geyer et al., 2002).

It is not clear that genes associated with lower vs. higher levels of basal PPI will be related to reduced PPI in schizophrenia or other disease states. The most potent physiological influence on acoustic PPI is hearing threshold, since an organism must detect an acoustic prepulse in order to exhibit acoustic PPI. Strain differences in age-related hearing changes have been identified among commonly studied mouse strains (Ouagazzal et al., 2006). Beyond this level of sensory

registration, the most potent neural influence on PPI is exerted at the level of the pedunculopontine nucleus (PPTg) (cf. Koch and Schnitzler, 1997), which mediates PPI via its impact on the NRPC. Thus, genetic studies of PPI will likely be influenced strongly by genes coding for hearing threshold and the normal function of the PPTg. In contrast, ventral forebrain DAergic substrates – which are suspected to be a critical substrate for some forms of psychopathology – are likely to be 3 or 4 synapses removed from the primary startle circuit. For this reason, in a normal human or rodent, genes regulating ventral forebrain DA activity will likely contribute only weakly to any gene mapping a "signal" based on levels of PPI. Importantly, the present studies were not designed to "map basal PPI genes" (a goal for which rats, and particularly outbred SD rats, would be ill-equipped), but rather to understand the biology (specifically, the generational transmission) of a neurochemically specific phenotype – sensitivity to the PPI-disruptive effects of DA stimulation – that has been elucidated primarily in outbred rats (cf. Koch and Schnitzler, 1997), and which has been shown to remain stable in outbred SD rats across more than a decade of genetic drift (Swerdlow et al., 2001b).

A number of consistent patterns emerged from the present studies that are largely confirmatory of past reports. For example, rat strain differences in the amount of startle magnitude were not linked to differences in PPI (Acri et al., 1995), and drug effects on these two measures were also separable (Swerdlow et al., 1986; cf. Swerdlow et al., 2000). In each of the three distinct test sessions in this study, startle magnitude of the F1s was comparable to that of BN rats, while the PPI phenotype was either intermediate between the SD and BN strains, or was most comparable to the SD phenotype. Furthermore, strain differences in PPI remained robust and qualitatively similar whether startle stimuli elicited significant strain differences in startle magnitude, or elicited no significant differences in startle magnitude (e.g. with 118 dB(A) pulses for SD rats vs. 105 dB(A) pulses for BN and F1 rats in the low/high pulse session). Finally, sensitivity to the effects of APO on startle magnitude across these strains (SD>F1>BN) did not correspond to sensitivity to the effects of APO on PPI (F1>SD>BN).

Sex differences in PPI have been noted in some but not in other published reports, and may be both species- and strain-dependent (Swerdlow et al., 1993, 1997; Lehmann et al., 1999; Plappert et al., 2005; Aasen et al., 2005). Across the three test sessions in this study, these differences were reliable and strain-specific, with F1s exhibiting robust sex differences in PPI (male>female), BNs exhibiting no significant sex differences, and SD rats exhibiting intermediate male>female differences. Because this is the same strain pattern observed for APO sensitivity (F1>SD>BN), one could reasonably speculate that the sex differences in PPI observed here – as in other behaviors (Blanchard et al., 1993; Becker, 1999; Fagergren and Hurd, 1999) – may be mediated in part via DAergic substrates.

The neural basis for an inherited vulnerability to the gating-disruptive effects of DA activation might be very relevant to inherited human brain disorders characterized by DA-sensitive gating deficits. In outbred SD, LE and F1 (SD × LE) strains, the inherited phenotype of PPI sensitivity to DA agonists is mediated by DA-linked signal transduction pathways within the ventral forebrain (Swerdlow et al., 2006a; Saint Marie et al., 2006). Clearly, pedigrees from different strains demonstrate different patterns of inheritance of PPI phenotypes, and the present findings demonstrate that patterns of generational transmission of the PPI APO sensitivity phenotype cannot be generalized across all rat strains. While the PPI phenotypes produced by the SD × BN cross suggest a biological regulation more complex than previously identified in SD and LE rats, the clear shift to greater APO sensitivity in the current F1s suggests some modification at, or beyond, D2- and perhaps D1-family receptors. Indeed, there is an increasing evidence that the post-DA receptor signal cascade is an important substrate for genetic and epigenetic events that enhance the DA "disruptability" of sensorimotor gating, and conceivably, contains targets by which antipsychotics normalize gating levels (Culm et al., 2004; Gould et al., 2004; Kanes et al., 2006; Kelly et al., 2007; Sotoyama et al., 2007). Whether these same substrates play a role in the pathogenesis of human disorders of impaired gating, or in the clinical therapeutic effects of medications, are logical next questions raised by these findings.

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