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Antipsychotic Effects on Prepulse Inhibition in Normal 'Low Gating' Humans and Rats

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Development of new antipsychotics and their novel applications may be facilitated through the use of physiological markers in clinically normal individuals. Both genetic and neurochemical evidence suggests that reduced prepulse inhibition of startle (PPI) may be a physiological marker for individuals at-risk for schizophrenia, and the ability of antipsychotics to normalize PPI may reflect properties linked to their clinical efficacy. We assessed the effects of the atypical antipsychotic quetiapine (12.5 mg po) on PPI in 20 normal men with a 'low PPI' trait, based on PPI levels in the lowest 25% of a normal PPI distribution. The effects of quetiapine (7.5 mg/kg s.c.) on PPI were then assessed in rats with phenotypes of high PPI (Sprague Dawley (SD)) and low PPI (Brown Norway (BN)); effects of clozapine (7.5 mg/kg i.p.) and haloperidol (0.1 mg/kg s.c.) on PPI were also tested in SD rats. At a time of maximal psychoactivity, quetiapine significantly enhanced PPI to short prepulse intervals (20–30 ms) in 'low gating' human subjects. Quetiapine increased PPI in low gating BN rats for prepulse intervals <120 ms; this effect of quetiapine was limited to 20 ms prepulse intervals in SD rats, who also exhibited this pattern in response to clozapine but not haloperidol. In both humans and rats, normal 'low gating' appears to be an atypical antipsychotic-sensitive phenotype. PPI at short intervals may be most sensitive to pro-gating effects of these drugs.
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INTRODUCTION

Clinical trials for antipsychotics in schizophrenia patients and individuals at high risk for developing this disorder are difficult due, among other reasons, to complexities associated with subject acquisition, potential medication interactions, risks of clinical relapse, and need for sustained treatment. These issues will be compounded further, as studies begin to explore the utility of the prophylactic use of novel antipsychotics in populations who are at increased risk of developing schizophrenia, based on a family history of schizophrenia or the presence of subclinical premorbid symptoms. Antipsychotic development would be greatly facilitated by physiological markers or 'bioassays' that are predictive of novel antipsychotic properties, and that can be applied in normal control populations.

One physiological 'marker' associated with schizophrenia is deficient prepulse inhibition (PPI) of the startle reflex. PPI is the normal reduction in startle that occurs when the startling stimulus is preceded 30–300 ms by a weak prestimulus (Graham, 1975). PPI is deficient in schizophrenia patients and unaffected relatives (Braff *et al*, 1978; Cadenhead *et al*, 2000; cf Braff *et al*, 2001)—indicating that it is a trait marker for individuals at-risk for developing the disorder (rather than a marker of schizophrenia *per se*)—and the neurobiological and genetic bases of this deficit are being actively studied. Some groups have reported that PPI levels in schizophrenia patients are at least partially restored by sustained treatment with antipsychotics, particularly those with clinically 'atypical' properties (Kumari *et al*, 1999; Weike *et al*, 2000). This suggests that the reversal of PPI deficits by atypical antipsychotics may reflect brain mechanisms relevant to their clinical properties.

PPI is also measured in infrahumans, and atypical antipsychotics oppose the PPI-disruptive effects of pharmacological (eg dopamine (DA) agonists, NMDA antagonists), surgical (eg adult lesions of the basolateral amygdala or neonatal lesions of the ventral hippocampus), or developmental (eg isolation rearing) challenges (Swerdlow *et al*, 1994a; cf Swerdlow *et al*, 2000; Geyer *et al*, 2001). Most relevant to the present study, some atypical antipsychotics (eg quetiapine and clozapine) are capable of increasing basal levels of PPI in rats and mice under conditions that elicit submaximal levels of PPI (eg weak prepulses, prepubertal age) (Swerdlow and Geyer, 1993; cf Geyer *et al*, 2001). Importantly, this suggests that antipsychotics modify processes responsible for the normal regulation of

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sensorimotor gating, and not simply its disruption by pathological states. It is thus possible that the enhancement of 'submaximal' gating in humans might serve as a useful and resource-efficient assay for predicting the clinical properties of antipsychotics, even in normal populations.

Relatively little is known about the effects of antipsychotics on PPI in normal human subjects. Published studies using the typical antipsychotic haloperidol have reported either no effect or PPI-reducing effects of this drug, consistent with observations in infrahumans (Abduljawad *et al*, 1998; Kumari *et al*, 1998; Oranje *et al*, 2004; cf Braff *et al*, 2001). These reports utilized a range of experimental conditions, including pure tone noises (Graham *et al*, 2004) and a range of prepulse intensities (Kumari *et al*, 1998; Oranje *et al*, 2004), but did not utilize test populations that would yield submaximal levels of PPI. We previously reported that 12.5 mg of quetiapine had no significant effects on PPI (10–120 ms intervals) in a between-subject study of 20 normal men (Wasserman *et al*, 2002); this was also observed by Graham *et al* (2004), with both 12.5 and 25 mg doses of quetiapine.

One potentially novel strategy for detecting antipsychotic effects on PPI would be to utilize a normal clinical population that exhibits the 'trait' marker of relatively low PPI levels, based on the range of a normal distribution of PPI levels. While we know neither the physiological nor genetic bases for the 'low PPI' trait in normal populations, this trait might be viewed as a surrogate marker for the reduced PPI in clinical populations. To date, no published reports have assessed the effects of clinically atypical antipsychotics on PPI in normal human subjects who exhibit a low PPI trait.

Experiment 1 assessed the effects of the atypical antipsychotic quetiapine on PPI in 20 clinically normal human subjects who exhibit a 'low PPI trait'. Quetiapine was selected for studies in normal subjects based on our past experience (Wasserman *et al*, 2002), lack of association with rare but severe side effects observed with other atypical antipsychotics (Idanpaan-Heikkila *et al*, 1975; Wirshing *et al*, 1998), and 'clozapine-like' profile in preclinical studies of PPI (Swerdlow *et al*, 1994b, 1996). Analyses attempted to identify correlates or predictors of quetiapine effects on PPI in normal subjects with a 'low PPI' trait. Experiment 2 assessed the effects of quetiapine on PPI in two strains of rats with high *vs* low PPI phenotypes, in a test session identical to that used in human studies. Additional experimentation was used to determine whether these drug effects were evident with other antipsychotics.

EXPERIMENT 1

The effects of quetiapine on acoustic startle and PPI were assessed in normal 'low gating' men.

Methods

Normal right-handed 18–35 years old men were recruited by local advertising. Phone screening excluded subjects endorsing a history of substance abuse or other mental illness, schizophrenia in a first-degree relative, other significant medical illness (eg cancer, diabetes, heart disease, HIV), current medications, history of seizure, open head injury or closed head injury with loss of consciousness >1 min, R-hand injury, or hearing or visual impairment. Appropriate subjects completed a screening visit, in which phone questions (above) were repeated, together with detailed demographic, medical, neurologic, and psychiatric screening (SCID-NP; First *et al*, 1997); subjects completed urine toxicology and EKG and hearing tests (exclusion: impairment at 40 dB(A), 1 Khz). Informed consent was obtained (UCSD IRB #031317). Subjects also completed the Tridimensional Personality Questionnaire (TPQ; Cloninger, 1987) and the Sensation Seeking Scale (SSS; Zuckerman and Link, 1968). A screening startle session was conducted (see below). At the end of this visit, subjects who exhibited $<16\%$ PPI (mean across 60 ms prepulse conditions; 'low gaters'; Figure 1) were scheduled to return 7 days ('week 1') and 14 days ('week 2') later. The 16% 'cutoff' identified the lowest quartile within a distribution of PPI among 143 normal control subjects screened on this test session prior to and during the course of this study.

On the test days, urine toxicology was repeated, and subjects ate a standardized meal 45 min prior to pill ingestion. Test drug (placebo *vs* 12.5 mg quetiapine in balanced, crossover design) was dispensed by UCSDMC Pharmacy Services. Test subjects and test personnel were blind to drug condition. Testing on each day lasted a total of approximately 3 h, and was identical across test days except for the study medication (placebo *vs* quetiapine) (Table 1). Subjects remained under supervision for 7 h after pill ingestion.

Startle was measured with an SR-LAB PC computer monitoring system and custom EMG amplifier with a 1K Hz band pass filter. Subjects sat in a quiet room, with two Beckman miniature Ag-AgCl electrodes placed 1 cm lateral and inferior to the R and L external canthus, over the orbicularis oculi ($R<10$K), and a ground electrode behind the R ear, over the mastoid. Subjects wore Telephonics TDH-39P headphones, and looked at a point on the wall that allowed them to be comfortable with their eyes open. A 3 min 70 dB(A) background white noise acclimation period was followed by acoustic startle trials. Acoustic stimuli include (1) a 118 dB(A) 40 ms noise burst

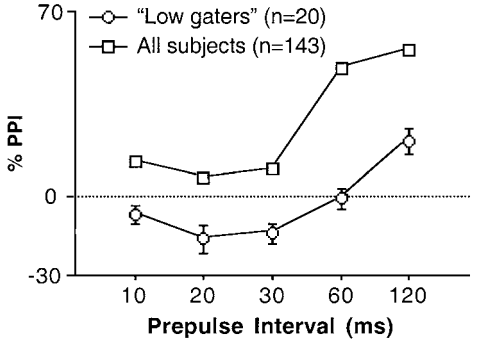

Figure 1 Mean %PPI (SEM) for 10–120 ms prepulse intervals in 20 subjects identified as 'low gaters' based on PPI levels in the lower quartile of a normative distribution in our laboratory, *vs* PPI in all subjects in this distribution.

Table 1 Test Schedule

Time (hours)	Event
0900	Heart rate/blood pressure/subjective rating scale
0915	Pill administration
0930	Heart rate/blood pressure/subjective rating scale
0940	PPI test 1
1000	Heart rate/blood pressure/subjective rating scale
1035	Heart rate/blood pressure/subjective rating scale
1045	PPI test 2
1105	Heart rate/blood pressure/subjective rating scale
1135	Heart rate/blood pressure/subjective rating scale
1145	PPI test 3
1205	Heart rate/blood pressure/subjective rating scale

(P-ALONE) or (2) 5 ms prepulses that were 16 dB above background. P-ALONE trials were presented either alone or 10–120 ms after a prepulse. After the screening session, subjects were excluded for mean R and L eyeblink P-ALONE startle magnitude <50 units.

The PPI session consisted of 42 active trials that included six conditions: a 118 dB(A) 40 ms noise burst presented alone (P-ALONE); and the same 118 dB(A) 40 ms noise burst preceded 10, 20, 30, 60, or 120 ms by a prepulse (5 ms noise burst) 16 dB above background. The session began and ended with three P-ALONE trials; a middle portion consisted of six repetitions of each of the six trials types (36 trials) in pseudorandom order. In addition, NOSTIM trials (signal acquisition but no stimulus presentation) were included between each pair of active trials. Testing began 25 min after pill administration ('TEST 1'), lasted approximately 15 min, and was repeated 90 min ('TEST 2') and 150 min ('TEST 3') after pill administration. Additional measures were obtained from all subjects, including a test of visual latent inhibition and perceived stimulus intensity; these data will be reported separately.

Subjective ratings (Table 2) were obtained via 100 mm visual analogue scales (VAS), assessing levels of specific somatic and psychological symptoms. These data were used to interpret bio- and psychoactivity of drug doses, as in appended reports (Swerdlow *et al*, 2002a, b, 2003a). Heart rate was recorded manually over a 15 s period. Systolic and diastolic blood pressure was recorded from the left arm manually via a sphygmomanometer, with subject sitting. Blink rate (BR) was assessed during each 3 min pre-startle acclimation period by trained observers (*R*'s among three observers >0.97) using a Radio Shack Security Camera (no. 49–2511) and monitor.

Data analyses primarily involved ANOVAs with drug dose as a within- or between-subject factors. Startle measures were analyzed separately at each time point (TEST 1, 2, and 3), based on differences in drug 'bioactivity' across the test session as suggested by symptom ratings. Two subjects during the second startle test exhibited mean startle magnitude on pulse-alone trials <10 units ('nonresponders') and thus were not included in the analysis of that startle test (inclusion of these subjects did not substantively alter the results of this test). Where dose group differences were detected in startle magnitude to P-ALONE stimuli, *post hoc* comparisons were pursued to examine effect sizes using subgroups matched for comparable P-ALONE startle magnitude. Ratings were treated as continuous variables and were analyzed with mixed-design ANOVAs. Alpha was 0.05.

Table 2 Subjective Rating Items (100 mm Visual Analog Scales)

1. Somatic	Queasy?
	Dizzy?
2. Emotional	Happy?
3. Consciousness	Drowsy?
4. Perceptual	Normal sounds seem unusually intense or loud?
	Cannot focus attention on one real sound or voice to the exclusion of others?

Results

Subject characteristics. Subjects were healthy, young, nonsmoking, college-educated, predominantly Caucasian, right-handed men. Based on their weight, the mean dose of quetiapine was approximately 0.17 mg/kg. Mean scores on the TPQ and SSS were within 0.5 SD of our published normative mean for this sample demographics (Swerdlow *et al*, 2003b) (Table 3). As reported previously (Swerdlow *et al*, 2003b), blink rate was elevated in low *vs* high gaters. Otherwise, low gaters did not differ significantly from high gaters (ie individuals in the upper three quartiles of the PPI distribution), when compared across a number of demographic, psychological, or physical characteristics (Table 3).

Autonomic measures. Quetiapine had no significant effects on heart rate (HR: $F=2.16$, df 1,19, NS), diastolic blood pressure (DBP: $F=1.65$, df 1,19, NS), or systolic blood pression (SBP: $F<1$). Both HR and SBP increased over the course of the testing period. Blink rate was also unaffected by quetiapine (effect of dose: $F<1$).

Subjective Rating Scales. The only rating scale that was sensitive to the effects of quetiapine was 'drowsiness'. ANOVA revealed a significant main effect of drug dose ($F=6.54$, df 1,19, $p<0.02$), a significant main effect of time ($F=7.24$, df 6,114, $p<0.0001$), and a significant interaction of dose $\times$ time ($F=8.24$, df 1,114, $p<0.0001$), reflecting significant increases in drowsiness by 55 min after quetiapine ingestion, peaking at 110 min after ingestion (Figure 2a). We examined whether quetiapine-induced drowsiness changed over test weeks. ANOVA revealed significant interactions of drug dose $\times$ test week ($F=6.96$, df 1,18, $p<0.02$), and of dose $\times$ time $\times$ week ($F=8.21$, df 6,108, $p<0.0001$). Quetiapine's effects on drowsiness were thus inspected separately for weeks 1 and 2. During test week 1, ANOVA revealed a significant interaction of drug $\times$ time ($F=7.57$, df 6, 108, $p<0.0001$), reflecting drowsiness that decreased across the session in placebo subjects, and increased across the session in quetiapine subjects, with significantly greater drowsiness in quetiapine

Table 3 Human Subject Characteristics: 'Low Gaters' *Vs* 'High Gaters'[a]

	Mean (range)	
	Low gater	**High gater**
Age (years)	22.6 (20–27)	23.0 (18–35)
Weight (kg)	73.9 (55.0–92.3)	78.6 (52.7–121.8)
Education (years)	14.9 (12–17)	14.4 (11–20)
	Mean (SEM)	
	Low gater	**High gater**
SSS[b]	21.1 (1.4)	22.6 (0.5)
NS total	16.2 (1.2)	17.8 (0.5)
HA total	7.5 (1.1)	8.6 (0.6)
RD total	18.6 (0.9)	18.8 (0.4)
Caffeine (mg/day)	72.0 (24.4)	96.9 (12.7)
Blink rate ($3\,min^{-1}$)	56.3 (7.7)	39.9 (2.7)
Ethnicity (C:A:H:AA)[c]	15:2:3:0	66:24:16:3
Eye color (% blue)	25	20

[a]All comparisons nonsignificant except Blink rate (low gater > high gater, $F = 5.47$, df 1,127, $p < 0.025$).
[b]Personality scales: SSS = sensation seeking scale; NS = TPQ novelty seeking; HA = TPQ harm avoidance; RD = TPQ reward dependence.
[c]C:A:H:AA = Caucasian:Asian:Hispanic:African American.

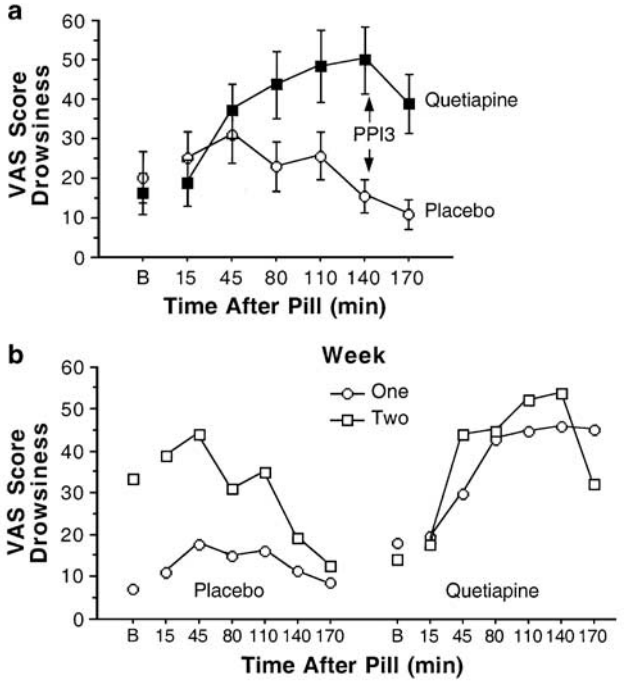

Figure 2 Mean VAS scores (SEM) for 'drowsy' self-ratings across the time course of testing, after ingestion of either placebo or quetiapine (12.5 mg). (a) Scores collapsed across the two test weeks show sedation building across the morning, peaking at the time of the third PPI test ('B' = baseline pre-drug measurement). (b) Scores separated into week 1 *vs* week 2, showing initial sedation evident after placebo during week 2, but not week 1.

vs placebo subjects during the second half of the test session (Figure 2b). In week 2, ANOVA revealed a significant main effect of drug ($F = 6.17$, df 1,18, $p < 0.025$) and a significant interaction of drug × time ($F = 3.21$, df 6,108, $p < 0.01$). Inspection of the data revealed that the main differences between weeks 1 and 2 resulted from greater drowsiness among placebo subjects during week 2 *vs* 1 (Figure 2b, left). Thus, quetiapine's effects on drowsiness *per se* did not change substantially across test weeks.

PPI. Consistent with our previous findings (Swerdlow *et al*, 2001a), the stability of the 'low gating' phenotype was evident in the significant correlation of PPI at the 60 ms prepulse interval (the basis for the 'low gating' group assignment) during the matching session and 60 ms PPI during the initial placebo test (all subjects ($n = 20$): $R = 0.49$, $p < 0.03$; subjects tested with placebo during first week ($n = 10$): $R = 0.64$, $p < 0.05$).

ANOVA of PPI revealed no significant effect of drug dose for Test 1, 2, or 3 (all $F < 1$), significant effects of prepulse interval for all tests ($F = 10.35$, 8.80 and 15.24, respectively), no significant dose × interval interactions for Test 1 or 2 ($F = 1.48$ and $F < 1$, respectively), and a near-significant interaction of dose × interval for Test 3 ($F = 2.23$, df 1,19, $p < 0.075$). This test took place at the time of maximal quetiapine-induced drowsiness. *Post hoc* analysis revealed that this interaction reflected a significant quetiapine-induced increase in PPI at the 20–30 ms intervals ($F = 4.61$, df 1,19, $p < 0.05$) (Figure 3a). There was also a significant effect of eye side during Test 3 ($F = 6.57$, df 1,19, $p < 0.02$), but no other significant two-, three-, or four-way interactions.

We next examined the impact of test order (active drug week 1 *vs* 2) on PPI during Test 3 (Figure 3b). ANOVA of PPI revealed a significant main effect of test week ($F = 6.68$, df 1,18, $p < 0.02$). Between-subject analyses of Test 3 PPI during week 1 ($n = 20$) revealed a significant main effect of quetiapine dose ($F = 5.50$, df 1,18, $p < 0.035$) and a significant interaction of dose × prepulse interval ($F = 2.51$, df 4,72, $p < 0.05$), reflecting quetiapine-induced increases in PPI for 10, 20, and 30 ms intervals. In contrast, a between-subject ANOVA of Test 3 PPI during week 2 ($n = 20$) revealed no significant effect of quetiapine ($F = 2.62$, df 1,18, NS) and no significant dose × interval interaction ($F < 1$). Inspection of the data (Figure 3b) revealed that the loss of a quetiapine *vs* placebo difference during week 2 reflected a persistent elevation of PPI among subjects who had received quetiapine during week 1, to levels that actually exceeded those of subjects who had ingested quetiapine during week 2. In other words, it appears that quetiapine's PPI-enhancing effects 'carried over' from week 1 to 2.

ANOVA of startle magnitude across all trials (P-ALONE and prepulse + pulse) revealed a significant overall reduction in startle magnitude after quetiapine treatment ($F = 8.21$, df 1,19, $p < 0.01$). To determine whether these startle-suppressing effects of quetiapine contributed to its PPI-enhancing effects, we assessed PPI in the subgroup of subjects ($n = 14$) who did not exhibit quetiapine-induced reductions in startle magnitude on P-ALONE trials (mean (SEM) magnitude placebo *vs* quetiapine = 93.20 (9.35) *vs*

92.04 (8.88)). The effect size (Cohen's *d* (Cohen, 1988)) for increased PPI during the 20–30 ms interval for this subgroup actually exceeded that for the full group of 20 subjects ($d = 0.44$ *vs* 0.34). Thus, the PPI-enhancing effects of quetiapine were not dependent on drug-induced reductions in startle magnitude.

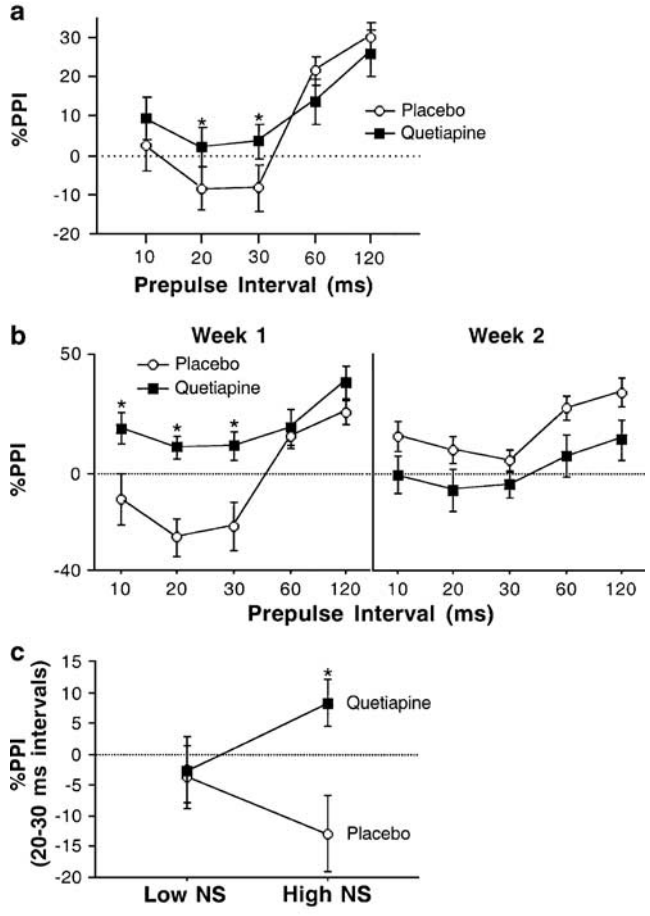

Figure 3 (a) Mean %PPI (SEM) for 10–120 ms prepulse intervals in 20 subjects during the third startle test, at a time of maximum quetiapine 'bioactivity' based on self-rated drowsiness. Short-interval PPI (20–30 ms intervals) was significantly increased by quetiapine. (b) Same data as in (a), separated into week 1 *vs* week 2. Quetiapine's PPI-enhancing effects were limited to week 1; PPI remained elevated in week 2 in subjects who received quetiapine during week 1. Screening levels of PPI did not differ between subjects assigned to receive quetiapine *vs* placebo during week 1 ($F < 1$). (c) Mean %PPI (SEM) for 20–30 ms intervals for subjects whose TPQ Novelty Seeking scores were in the upper *vs* lower 50%. Quetiapine's PPI-enhancing effects were limited to individuals with high NS scores. *Significantly greater than placebo, $p < 0.05$.

We next examined the relationship between quetiapine-induced drowsiness and PPI during Test 3. A difference score was calculated to determine the impact of quetiapine on drowsiness ratings immediately after Test 3. A median split (drowsiness means −0.3 (2.3) *vs* 45.6 (4.2)) ($F = 1.40$, df 1,18, NS) was then used as a grouping factor for the ANOVA of PPI for 20–30 ms intervals. ANOVA again revealed a significant effect of drug dose on PPI ($F = 4.44$, df 1,18, $p < 0.05$), but no effect of drowsiness level on PPI, and no significant interaction of drug × drowsiness ($F < 1$).

Finally, we assessed the relationship between personality dimensions and quetiapine PPI sensitivity. A median split strategy was again applied, this time to scores on scales of sensation seeking (SSS), novelty seeking (TPQ: NS), harm avoidance (TPQ: HA), and reward dependence (TPQ: RD). The relevant statistic was the interaction of subscale × drug dose. This interaction was not significant for SSS ($F < 1$), HA ($F < 1$), or RD ($F < 1$), but was significant for NS ($F = 4.36$, df 1,18, $p = 0.05$). This interaction reflected a significant quetiapine-induced potentiation of PPI in high NS individuals ($F = 8.45$, df 1,9, $p < 0.02$) but not in low NS individuals ($F < 1$) (Figure 3c). For the 30 ms PPI interval, the correlation (R) between NS score and quetiapine effect (active dose minus placebo) was 0.52 ($p < 0.02$). In contrast to changes in PPI, quetiapine-induced drowsiness did not differ between individuals with high *vs* low NS scores ($F < 1$).

Startle magnitude, habituation, and latency. ANOVA of startle magnitude on P-ALONE trials during PPI testing revealed no significant effect of quetiapine dose during TEST 1 and TEST 2 PPI tests (F's = 2.27 and 2.89, respectively, both NS), but a significant quetiapine-induced reduction in startle magnitude on P-ALONE trials during Test 3 ($F = 6.16$, df 1,19, $p < 0.025$) (Table 4). There was no significant correlation within individuals between the quetiapine-induced reduction in startle magnitude and increase in PPI for 20–30 ms prepulse intervals ($R = 0.07$, NS) or for 30 ms prepulse intervals alone ($R = 0.04$), nor were the startle-suppressing effects of quetiapine related to novelty seeking (NS) scores (dose × NS score interaction: $F = 1.40$, df 1,18, NS). Startle habituation was also unaffected by quetiapine in Tests 1 and 2 (dose × block interactions, F's = 1.41 and 1.78, respectively, both NS), but there was a significant quetiapine-induced increase in habituation in Test 3 (dose × block interaction: $F = 5.60$,

Table 4 Startle Magnitude in Human Subjects on P-ALONE Trials (Mean (SEM))

	Placebo			Quetiapine		
Test[a]	**Before PPI**	**During PPI**	**After PPI**	**Before PPI**	**During PPI**	**After PPI**
1	135.3 (14.5)	110.4 (12.7)	102.6 (13.8)	155.7 (14.5)	126.2 (14.0)	101.6 (11.9)
2	128.7 (12.9)	112.1 (11.2)	104.7 (10.8)	122.5 (12.7)	98.3 (11.2)	87.7 (10.5)
3	134.6 (13.6)	119.8 (12.8)	115.5 (13.6)	116.5 (11.3)	96.5 (10.8)[b]	79.9 (9.3)[c]

[a]Each test included three P-ALONE trials before PPI testing ('Before PPI') and three P-ALONE trials after PPI testing ('After PPI').
[b]Quetiapine suppressed P-ALONE magnitude during PPI testing, $p < 0.05$.
[c]Test 3: Quetipaine enhanced habituation ('Before' *vs* 'After') × drug interaction ($F = 5.60$, df 1,19, $p < 0.03$).

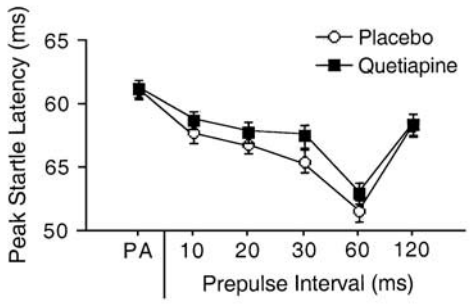

Figure 4 Peak startle latency (SEM) on P-ALONE (PA) and prepulse + pulse trials in Test 1. Findings in Tests 1–3 demonstrated normal latency facilitation for 10–60 ms prepulse intervals, with no significant effect of quetiapine.

df 1,18, $p<0.03$) (Table 4). The habituation-enhancing effect of quetiapine also did not correlate with its PPI-enhancing effect ($R=-0.09$), nor was it related to NS scores (dose × NS interaction: $F<1$). ANOVA of peak reflex latency revealed significant effects of trial type for all tests ($p<0.0001$ for Tests 1, 2, and 3), no significant effect of drug dose for any test (F's = 1.69, 2.11 and 1.69, respectively, all NS), and no significant interactions of dose × trial type for any test ($F<1$ for Tests 1 and 3, and $F=1.64$, df 5, 90, NS for Test 2) (Test 1 data is shown in Figure 4).

EXPERIMENT 2

Experiment 1 demonstrated that at a point of maximum psychoactivity, as suggested by its sedative and startle-suppressing properties, quetiapine increased short latency PPI in normal 'low gating' men. Experiment 2 examined the effects of quetiapine and other antipsychotics on short latency PPI in rats with 'high gating' (SD) and 'low gating' (BN) phenotypes.

Methods

Male SD ($n=47$) and BN ($n=17$) rats were obtained as adults from commercial suppliers (Harlan Laboratories; SD: San Diego, CA; BN: Indianapolis, IN). Rats received food and water *ad libitum* while housed in a climate-controlled facility with reverse 12-h light/dark cycle. All behavioral testing took place in the dark phase. Rats were handled within 48 h of arrival and allowed to acclimate to the laboratory for 7 days prior to behavioral testing. All experiments conform to the National Institutes of Health Guide for the care and use of laboratory animals (NIH Publications No. 85–23) and were approved by the Animal Subjects Committee at the University of California, San Diego (protocol #S01221).

Startle chambers (SR-LAB Startle Reflex System; San Diego Instruments, San Diego, CA) were located in a sound-attenuated room with 60 dB ambient noise. Rats were exposed to a 'matching' startle session used to assign rats to balanced drug groups according to their average level of PPI. Sessions were identical to those used in human testing in Experiment 1, except that the acclimation period was 5 min instead of 3 min, and prepulses were 15 dB over background, rather than 16 dB. Testing began 4 days after matching (week 1) and continued 7 days later (week 2), with dose reversed and treatment order balanced between rat strains. In one set of tests, SD ($n=17$) and BN rats ($n=17$) received either quetiapine (7.5 mg/kg, s.c.) or vehicle (saline/HCl; pH > 5.0) 10 min prior to PPI testing. In a second set of SD rats, a single test was used to compare the effects of clozapine (7.5 mg/kg in saline/HCl, pH > 5.0, i.p.; $n=10$; 10 min prior to testing), haloperidol (0.1 mg/kg s.c. in saline; $n=10$; 10 min prior to testing), and vehicle ($n=10$). In this second set of tests, trials were divided into two blocks to assess the time course effects.

Data analyses were comparable to those used in human testing in Experiment 1. Startle variables (startle magnitude, habituation, and PPI) were analyzed by repeated measures ANOVAs, with trial type and trial block as within-subject factors, and drug dose as within-subject (quetiapine) or between-subject (clozapine, haloperidol) factors; in the case of quetiapine, strain was also a between-subject factor. For clozapine and haloperidol, separate comparisons were made *vs* the same set of vehicle-treated rats. As with human studies, where group differences were detected in startle magnitude to P-ALONE stimuli, *post hoc* comparisons were pursued to examine effect sizes using subgroups matched for comparable P-ALONE startle magnitude. Alpha was 0.05.

Results

Prepulse inhibition. ANOVA of PPI in placebo-treated rats revealed a significant effect of prepulse interval ($p<0.0001$) and a significant strain × interval interaction ($F=12.74$, df 4,128, $p<0.0001$). *Post hoc* comparisons revealed significant BN > SD PPI for 10 ms prepulse intervals ($p<0.025$), and significant SD > BN PPI for 30, 60, and 120 ms prepulse intervals ($p<0.001$, 0.0001 and 0.003, respectively; Figure 5a). The stability of the 'low gating' phenotype was evident in the significant correlation of PPI at the 60 ms prepulse interval (the basis for the 'low gating' group assignment in Experiment 1) during the matching session and PPI during the initial vehicle test (all subjects ($n=34$): $R=0.55$, $p<0.001$; subjects tested with vehicle during first test day ($n=17$): $R=0.74$, $p<0.0008$).

Quetiapine increased PPI in BN rats across 20–60 ms prepulse intervals; SD rats exhibited only a modest increase in PPI, restricted to 20 ms prepulse intervals. ANOVA of PPI with quetiapine dose as a within-subject variable and drug week as a between-subject variable revealed a significant effect of quetiapine dose ($F=6.48$, df 1,30, $p<0.02$), a near-significant interaction of dose × drug week ($F=3.79$, df 1,30, $p<0.062$), and a significant interaction of dose × drug week × strain ($F=4.51$, df 1,30, $p<0.05$). *Post hoc* ANOVAs in rats receiving vehicle on week 1 revealed a significant effect of quetiapine ($F=8.79$, df 1,15, $p<0.01$), and a near significant interaction of strain × quetiapine ($F=4.15$, df 1,15, $p<0.06$). Separate ANOVAs among this subgroup revealed significant main effects of quetiapine in BN rats ($F=14.11$, df 1,7, $p<0.008$) but not SD rats ($F<1$). Inspection of the data (Figure 5b) revealed that quetiapine increased PPI in BN rats for prepulse intervals <120 ms,

while for SD rats, this effect was restricted to 20 ms prepulse intervals.

In contrast, rats receiving quetiapine during the initial week experienced no PPI-enhancing effects of this drug. This is reflected in a lack of main or interaction effects of quetiapine in these rats. Inspection of the data (Figure 5b) revealed that, as in Experiment 1, the lack of PPI-enhancing effects of quetiapine reflected in part the fact that PPI levels after vehicle treatment were elevated in rats that had previously been treated with quetiapine (compare BN/vehicle rats in Figures 4b, week 1 *vs* 2).

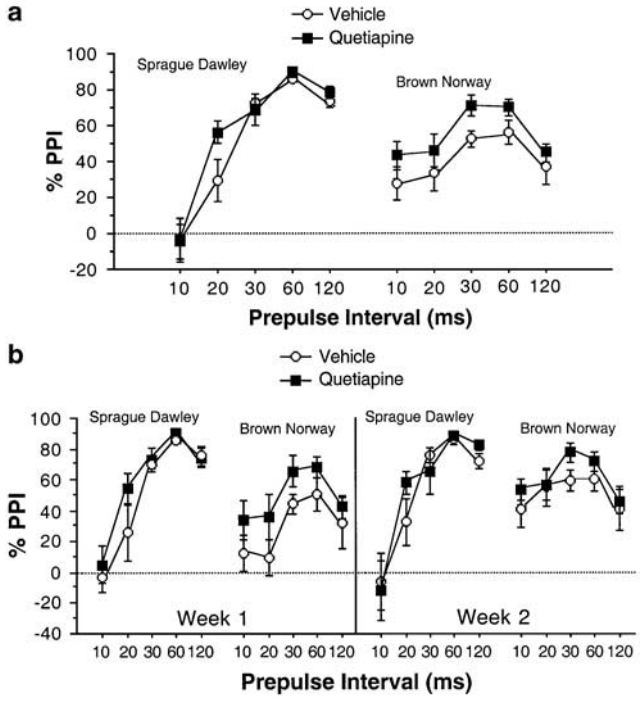

Figure 5 Mean % PPI for SD ($n=17$) and BN rats ($n=17$) treated with either vehicle or quetiapine (7.5 mg/kg). (a) BN rats exhibited significantly more PPI than SD rats for 10 ms prepulse intervals, and significantly less PPI than SD rats for 30–120 ms intervals. Quetiapine increased PPI in SD rats at 20 ms prepulse intervals, and in BN rats across much of the 10–120 ms temporal window. (b) Same data as in (a), separated into week 1 *vs* week 2. Quetiapine's PPI-enhancing effects were limited to week 1; PPI remained elevated in week 2 in BN rats that received quetiapine during week 1 (compare BN vehicle week 1 to BN vehicle week 2).

Analysis of startle magnitude on P-ALONE trials revealed significant effects of strain (SD > BN; $F=8.16$, df 1,32, $p<0.008$) and dose ($F=10.40$, df 1,32, $p<0.003$), but no interaction (Table 5). To assess the potential contribution of reduced startle magnitude to the PPI-enhancing effects of quetiapine, subgroups of rats were identified in which quetiapine did not reduce startle magnitude (SD rats: mean (SEM) P-ALONE magnitude for vehicle and quetiapine = 204.22 (52.28) and 205.83 (41.28), respectively; BN rats: mean (SEM) P-ALONE magnitude for vehicle and quetiapine = 119.10 (14.87) and 105.5 (5.54), respectively). Among these rats, effect sizes (Cohen's *d*) for quetiapine-induced increases in PPI were: SD rats, 20 ms prepulse intervals: 0.83; BN rats, 10, 20, 30, 60, and 120 ms prepulses intervals: 1.69, 2.00, 2.88, 0.90 and 0.64, respectively. Thus, among rats that did not exhibit startle-suppressing effects of quetiapine, the PPI-enhancing effects may have actually been more robust, and at the least, remained large to very large.

We next tried to determine whether the PPI-enhancing effects of quetiapine in rats reflect properties shared by other atypical antipsychotics. ANOVA of PPI with clozapine dose as a between-subject factor revealed a significant effect of prepulse interval ($p<0.0001$) and a significant dose × interval interaction ($F=2.54$, df 4,72, $p<0.05$), reflecting clozapine-induced increase in PPI at the 20 ms prepulse interval ($p<0.025$). There were no significant effects of trial block on PPI, or interactions of block × drug, or block × drug × interval (all F's < 1). In contrast, ANOVA of PPI in response to the typical antipsychotic, haloperidol, resulted in no significant main effects of dose, and no significant dose × interval interaction (Figure 6). There was also no significant effect of trial block on PPI ($F<1$), or interaction of block × drug ($F=1.68$, df 1,18, NS). A significant three-way interaction of block × drug × interval ($F=3.62$, df 4,72, $p<0.01$) reflected a nonsignificant haloperidol-induced reduction in PPI at 10 ms prepulse intervals in the first PPI trial block ($F=1.69$, df 1,18, NS; $d=0.60$), and a nonsignificant haloperidol-induced increase in PPI at 20 ms prepulse intervals in the second PPI trial block ($F<1$; $d=0.42$). In the case of clozapine, a trend towards

Table 5 Startle Magnitude in Rats on P-ALONE Trials during PPI Testing (Mean (SEM))

		Vehicle			Quetiapine[a]		
Strain[b]	**Number**	**Before PPI**	**During PPI**	**After PPI**	**Before PPI**	**During PPI**	**After PPI**
SD	($n=17$)	614.9 (71.0)	275.6 (49.0)	375.3 (74.5)	641.4 (76.0)	186.1 (26.6)	182.7 (33.2)
BN	($n=17$)	392.9 (48.8)	181.5 (22.4)	134.1 (13.6)	178.8 (19.2)	93.4 (6.5)	71.2 (8.2)

Strain	**Drug**	**Before PPI**	**During PPI**	**After PPI**
SD	Vehicle ($n=10$)	520.3 (82.5)	223.1 (35.4)	177.3 (30.6)
SD	Clozapine ($n=10$)	288.9 (66.1)	113.4 (20.5)	162.0 (35.2)
SD	Haloperidol ($n=10$)	410.9 (46.2)	148.8 (13.7)	141.0 (12.4)

[a]Main effect of drug (quetiapine < vehicle) on startle magnitude during PPI ($p<0.003$), and in Before/After PPI blocks ($p<0.002$).
[b]Main effect of strain (SD > BN) on startle during PPI ($p<0.008$), and in Before/After PPI blocks ($p<0.0001$).

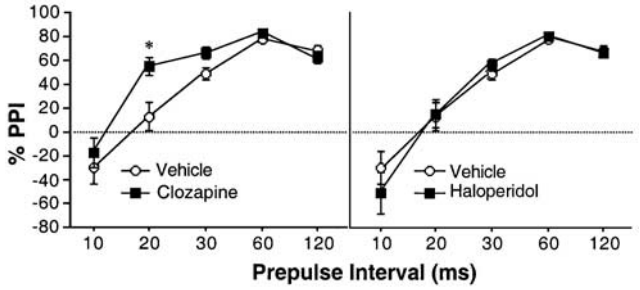

Figure 6 Mean %PPI in rats treated with vehicle ($n = 10$), clozapine (7.5 mg/kg; $n = 10$), or haloperidol (0.1 mg/kg; $n = 10$). PPI was significantly increased by clozapine at the 20 ms prepulse interval ($p < 0.025$). Note: only one group of rats was treated with vehicle, and these data are seen on both left and right sides of Figure 6. *Significantly greater than vehicle, $p < 0.025$.

startle-suppressing effects ($F = 3.66$, df 1,18, $p < 0.075$) triggered a precautionary assessment of PPI in subgroups matched for identical startle magnitude (mean (SEM) vehicle: 143.10 (16.34); clozapine: 150.20 (22.86)). As with quetiapine, this approach appeared to strengthen the ability to detect PPI-enhancing effects (main effect of dose: $F = 6.38$, df 1,12, $p < 0.03$; dose × interval interaction: $F = 5.07$, df 4,48, $p < 0.002$; d for 20 ms PPI = 2.89).

DISCUSSION

The present studies demonstrated that under specific conditions, atypical antipsychotics enhance short-latency PPI in humans and rats, particularly in cohorts of both species that normally exhibit low levels of PPI. The generalizability of these findings may be limited by the use of only a single drug dose, and in humans, by the use of only a single drug. In particular, the dose of quetiapine used in humans in Experiment 1 (12.5 mg) is well below the therapeutic range for clinical antipsychotic efficacy; nonetheless, even this small dose in normal subjects resulted in significant sedation and reduction of startle magnitude, consistent with previous reports (Wasserman *et al*, 2002; Graham *et al*, 2004).

In humans, this low but physiologically active dose of quetiapine increased short-interval PPI among normal men who were characterized by low basal levels of PPI. These effects were most evident during the first week of a crossover design, apparently due to persistent or 'carry-over' increases in PPI in subjects who had received quetiapine during the first week of testing. In fact, during the second week of testing, short-interval PPI in these 20 subjects was 'corrected' to levels comparable to that of the upper 75% of the normal distribution (Figure 1). In other words, to the degree that low levels of short-interval PPI is a physiological trait—and the present study provides evidence for its stability prior to antipsychotic exposure—it is 'recalibrated' for at least 1 week by a single exposure to a very small dose of quetiapine. In contrast, long latency PPI remained at very low levels in the second week of testing of 'low gating' individuals.

These drug effects were evident only at the time point of maximal drug 'psychoactivity', as indicated by peak sedation, reduced startle magnitude, and enhanced startle habituation. Interestingly, the PPI-enhancing effects of quetiapine were not correlated with the amount of subjective sedation reported by the subjects, the amount of startle suppression caused by quetiapine, or the potentiation of habituation by quetiapine, suggesting that these processes shared a common time course, but were otherwise mediated by separate mechanisms.

A secondary aim of Experiment 1 was to examine personality dimensions that might be associated with a greater sensitivity to quetiapine effects on PPI. There was a clear relationship between high NS scores and greater sensitivity to the PPI-enhancing effects of quetiapine. High NS scores have been conceptually related to extraversion and specific DA receptor polymorphisms (Becker *et al*, 2005). It is conceivable that differences in DA receptor function associated with higher NS scores might contribute to greater sensitivity to quetiapine's effects on PPI. Certainly, such a relationship would be better pursued in a larger population, with a greater range of NS values.

Previous studies have reported reduced PPI in individuals affected by any one of several neuropsychiatric disorders, as well as unaffected family members of schizophrenia probands (Castellanos *et al*, 1996; Gomez-Wong *et al*, 1998; Swerdlow *et al*, 1993, 1995b; Braff *et al*, 2001). Importantly, the 'low gating' individuals in the present study were clinically normal, and carefully screened to rule out psychopathology, a family history of severe mental illness, and recreational drug use. Certainly, our findings might have differed had the study sample included individuals with subclinical psychotic symptoms or a positive family history of schizophrenia. The present 'low gaters' also did not differ significantly from our historical 'normal gating' sample, on the basis of demographics or scores in the SSS or TPQ. We have previously noted no relationship between PPI levels (using stimulus parameters identical to the present study) and SSS or TPQ scores (Swerdlow *et al*, 2003b), although we have reported other personality inventories that identify cohorts with relatively reduced PPI levels (Swerdlow *et al*, 1995a).

The notion that PPI drug sensitivity in clinically normal subjects might be influenced by basal levels of PPI is consistent with previous findings from our laboratory and others. For example, we reported that the indirect dopamine agonist amphetamine reduced PPI only in normal adult males who exhibited baseline PPI levels in the upper 50% of a normal population (Swerdlow *et al*, 2003a), and a similar finding was reported by Bitsios *et al* (2005) using the dopamine agonists pergolide and amantadine. That the present finding detected essentially the opposite pattern (increased PPI among low gating individuals) using a dopamine antagonist supports the contention that dopamine function can truly modulate (ie decrease or increase) sensorimotor gating, depending on a 'set-point' level of gating function. There is no immediate way to determine whether the mechanisms responsible for quetiapine-induced increases in PPI among 'low gating' normal individuals are in any way related to the ability of atypical antipsychotics to increase PPI in 'low gating' schizophrenia patients (Kumari *et al*, 1999; Weike *et al*, 2000).

Short-interval (10–30 ms) PPI is thought to reflect the most automatic or preconscious form of startle gating, as it is not sensitive to directed attention (Bohmelt *et al*, 1999;

Filion *et al*, 1993). The present findings suggest that a low dose of an atypical antipsychotic can selectively enhance this preconscious inhibitory process, but does not enhance longer interval gating processes. The insensitivity of PPI at 120 ms prepulse intervals to quetiapine was also reported by Graham *et al* (2004), using pure tone background, prepulse and pulse stimuli. In laboratory animals, short-interval PPI exhibits a very distinct pattern of pharmacological sensitivity, compared to longer interval PPI. For example, in albino SD rats, short-interval PPI is enhanced by atypical antipsychotics (present data: quetiapine and clozapine), low doses of direct DA receptor agonists (eg pergolide (Swerdlow *et al*, 2001b)), and D1 antagonists (SCH23390; Swerdlow *et al*, 2004). Some evidence suggests that distinct neural and genetic substrates regulate short- *vs* long-interval PPI in rodents (Hince and Martin-Iverson, 2005; Swerdlow *et al*, 2004), and the present study might suggest that the substrates that normally regulate short-interval PPI might be particularly informative regarding the mechanisms of action of atypical antipsychotics.

A legitimate question remains, however, as to whether the PPI-enhancing effects of quetiapine and clozapine at short prepulse intervals in the present studies relate to timing-specific neural mechanisms, or instead simply reflect the low levels of PPI elicited at these intervals. We previously reported that clozapine increased low levels of PPI in SD rats elicited by weak prepulse (1–5 dB over background) at longer prepulse intervals (100 ms) (Swerdlow and Geyer, 1993). Findings in BN rats in the present study also argue that, at least in this inbred strain with low basal levels of PPI, the PPI-enhancing effects of quetiapine are evident across most prepulse intervals. On the other hand, neither quetiapine nor clozapine increased PPI in SD rats at 10 ms prepulse intervals, despite even lower levels of PPI at this shorted interval, compared to the 20–30 ms intervals; this would argue against an effect of antipsychotics based solely on low levels of PPI. Other studies in humans have demonstrated that haloperidol does not enhance PPI, using relatively weak prepulses that elicit submaximal levels of PPI (Kumari *et al*, 1998; Oranje *et al*, 2004). While this issue remains under active study, it is at least fair to say that prestimulus parameters are important determinants not only of basal PPI characteristics but also of drug effects on PPI (Swerdlow *et al*, 2004).

Previous studies have reported reduced PPI in BN rats, compared to other inbred or outbred rat strains (Palmer *et al*, 2000; Conti *et al*, 2005). The present findings, however, suggest that such a characterization is not fully informative: depending on the prepulse interval, BN rat exhibited more (10 ms intervals), the same amount (20 ms intervals) or less PPI (30–120 ms intervals), compared to SD rats. Thus, the genetic and neural differences responsible for PPI differences in BN *vs* other rat strains do not simply result in a 'low gating' animal, but instead, one whose PPI deviates from 'excessive' (10 ms intervals: $d = 0.83$) to 'deficient' (120 ms intervals: $d = 1.24$), depending on the temporal parameters being probed. Furthermore, while Conti *et al* (2005) reported that PPI with 100 ms intervals in BN rats is not increased by the atypical antipsychotic clozapine, the present findings suggest that shorter prepulse intervals (10–60 ms) might exhibit such sensitivity, based on the effects of quetiapine. We have already demonstrated that, at least in some cases, it is the temporal characteristics of inhibition—rather than the overall magnitude of inhibition *per se*—which is the heritable phenotype distinguishing rat strains (Swerdlow *et al*, 2004). Importantly, this does not appear to be the case in schizophrenia, where the phenotype of reduced PPI is evident at 30, 60, and 120 ms prepulse intervals (cf Braff *et al*, 2001). Thus, it is certainly conceivable that the genes and neural substrates identified based on differences in the temporal regulation of PPI between specific rat strains (eg BN *vs* SD) may not be particularly relevant to the genetic and neural mechanisms responsible for the loss of PPI in schizophrenia.

Compared to SD rats, BN rats are not 'low gating' across the entire span of 10–120 ms prepulse intervals, but they are 'low gating' at the 60 ms interval—the phenotype used to define 'low' *vs* 'high' gating humans in Experiment 1. One might thus argue that the SD *vs* BN data parallel the findings in humans in Experiment 1: 'low gating' BN rats appear to be particularly sensitive to the PPI-enhancing effects of quetiapine. However, a number of strain differences, other than basal PPI levels at 60 ms prepulse intervals, might account for differential quetiapine sensitivity in BN *vs* SD rats. We did not detect evidence that, independent of strain, the 'low gating' phenotype conferred greater antipsychotic sensitivity in rats. For example, Experiment 1 defined 'low gating' based on the lowest quartile in a normal population; applying this approach to Experiment 2 yielded samples of $n = 4$ or less. Nonetheless, among SD rats, those in the lowest quartile of basal PPI were not most sensitive to the PPI-enhancing effects of quetiapine, clozapine, or haloperidol, and among BN rats, those in the lowest quartile of basal PPI were not most sensitive to the PPI-enhancing effects of quetiapine.

Quetiapine effects on PPI in BN and SD rats also underscore another feature of PPI: the lack of association between PPI and startle magnitude on P-ALONE trials. Thus, compared to SD rats, BN rats exhibit reduced levels of startle magnitude, and reduced levels of PPI. Quetiapine further reduced startle magnitude in BN rats, but actually increased PPI levels. Thus, low basal levels of startle magnitude are associated with reduced PPI, but low drug-induced levels of startle magnitude are associated with elevated PPI. This is not to suggest that startle magnitude cannot be an important determinant of PPI: any change in % PPI in the context of changes in startle magnitude should prompt efforts to assess the potential relationship of these changes, as was done in both human and rat studies described herein. In the case of BN rats, the findings provide a clear 'dissociation': reduced startle magnitude is associated with both lower and higher levels of PPI.

One major goal of this study was to determine whether antipsychotic effects on PPI in low gating normal humans might be a useful screening measure of predicting clinical efficacy. A dispassionate view of the present findings would argue against such an approach, based on the small effect size ($d \approx 0.4$), dose-limiting side effects of sedation and reduced startle magnitude, and labor-intensive process of screening a large normal sample to identify a 'low gating' cohort. Furthermore, with the exception of the personality correlates and subjective drug effects, much of the information yielded in this human study—which required well over a year for data acquisition—could be gleaned

from studies in rodents, which were completed much faster and at much less expense. Certainly, some experimental questions of clinical relevance are best assessed in studies with human subjects, but the present findings do not provide compelling evidence that this applies to predictive studies based on PPI-enhancing effects of antipsychotics.

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