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Sensory and sensorimotor gating-disruptive effects of apomorphine in Sprague Dawley and Long Evans rats

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Abstract

Rationale—Rat strains differ in sensitivity to the disruptive effects of dopamine agonists on sensorimotor gating, measured by prepulse inhibition (PPI) of startle. For example, Sprague Dawley (SD) rats are more sensitive to PPI-disruptive effects of apomorphine (APO) compared to Long Evans (LE) rats; F1 (SD × LE) and N2 generations exhibit intermediate phenotypes. We reported that APO increased S2/S1 ratios and reduced S1 amplitudes of the N40 event-related potential (ERP) in SD rats, suggesting that it reduced sensory gating and/or sensory registration. Here, we investigated whether SD and LE rats differ in sensitivity to APO effects on N40 gating or amplitude.

Methods—PPI and N40 gating were assessed in male SD and LE rats after APO, in a 4 day within-subject design.

Results—Compared to SD rats, LE rats were less sensitive to the PPI-disruptive effects of APO. APO increased S2/S1 ratios paralleled by a dose-dependent reduction in S1 amplitude; SD and LE rats did not differ significantly in this measure. No clear relationship was evident between APO effects on PPI and N40 gating, nor between APO effects on startle magnitude and S1 amplitude, across strains.

Conclusion—SD and LE rats differ in their sensitivity to the disruptive effects of dopamine receptor activation on sensorimotor gating (PPI) but not sensory gating (N40 suppression) or sensory registration (S1 amplitude). These data suggest differences in both the neural and genetic regulation of dopamine agonist effects on these measures.

Keywords

apomorphine; dopamine; prepulse inhibition; schizophrenia; sensory gating; sensorimotor gating; startle – strain

Introduction

Both prepulse inhibition (PPI, a measure of sensorimotor gating) and P50 event-related potential gating (ERP, a measure of sensory gating) paradigms assess the inhibitory impact of

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a lead stimulus on the central nervous system response to a second stimulus. Schizophrenia patients exhibit heritable deficits in both PPI and P50 ERP gating [1,6,17]). Consequently, both PPI and P50 gating are being used as endophenotypes to identify vulnerability genes for this disorder [5,8,17,49].

PPI and ERP-based gating measures can be acquired in rodents. In some cases, there are heritable differences in either baseline levels of gating (e.g. in Brown Norway vs. Wistar or Sprague Dawley rats; [25,36]) or the sensitivity to the loss of gating induced by pharmacological manipulations [9,42,44,46]. These heritable patterns are being used in translational studies of the neurobiology and genetics of gating deficits in schizophrenia. In one model, albino Sprague Dawley (SD) rats are more sensitive to the PPI-disruptive effects of dopamine (DA) agonists, compared to hooded Long Evans (LE) rats. These strain differences are heritable, neurochemically specific, and associated with differences in D2-linked signal transduction pathways in the nucleus accumbens, along with specific differences in gene expression in this region [30, cf 48].

We previously reported that gating of the N40 ERP in SD rats is disrupted by the DA agonist, apomorphine (APO) [38]. Conceivably, sensitivity to this drug-induced loss of “gating” – like the APO-induced loss of PPI – might also be heritable in rats. This would be important to determine, because N40 gating in rodents is proposed by some (though certainly not all, e.g. see Connolly et al. [9]) to be an analog of the P50 ERP in humans, and the heritable loss of P50 ERP gating in schizophrenia is a powerful phenotype that has already been linked to a specific gene [15]. Thus, an animal model of heritable N40 gating “disruptability” might be a valuable tool for studying the neural basis for the genetic regulation of an important endophenotype of schizophrenia.

However, there are substantive differences in the neurochemical regulation of PPI and N40 gating (as reviewed in Swerdlow et al. [38]), and thus it is not intuitively obvious that N40 gating and PPI share either a common neurobiology or similar patterns of strain sensitivity. As an initial step to assess commonality in the genetic control of the DAergic regulation of PPI and N40 gating, we examined whether similar SD vs. LE strain differences were evident in the DAergic regulation of PPI and N40 gating, measured contemporaneously in the same rats.

Methods

Studies were conducted in accordance with the "Principles of laboratory animal care" (NIH publication No. 86-23, revised 1985) and were approved by the UCSD IACUC Committee. Adult male SD (n = 28) and LE (n = 29) rats (225–250 g; Harlan, Livermore, CA) were housed in a temperature controlled room, in groups of 2–3, on a reversed 12 h:12 h light/dark schedule with *ad lib* food and water. Rats were handled individually within 48 h of arrival and again one week post-surgery. Surgery occurred 7–10 days after arrival. All efforts were made to minimize rat suffering and reduce the number of rats used. All experiments conform to guidelines of the National Institute of Health for the use of rats in biomedical research (NIH Publications No. 80-23) and were approved by the Animal Subjects Committee at UCSD (protocol #S01221).

Surgical preparations: Prior to surgery an uncut tri-pole electrode (Plastics-One, Roanoke, VA) was modified. A Jam Nut fastener (Plastics-One) was placed on the head plug for precise placement of the connector cable (Plastics-One; 100 cm TT2). Rats received 0.1 ml atropine sulfate subcutaneously (sc) (Vedco Inc. St Joseph, MO. 0.054 mg/ml) 15–30 min before full anesthesia with sodium pentobarbital intraperitoneally (ip) (Abbott, 60 mg/kg). They were secured in a Kopf stereotaxic instrument (Tujunga, CA) in a flat skull position (tooth bar 3.3 mm below interaural line). A 2 cm incision exposed the skull, and the bone surface was cleaned.

Two holes were drilled for ground wire placement on dura, approximately 1 mm anterior to Bregma and 1 mm lateral of the midline suture. Three holes were drilled for anchor screws (Plastics One), and another for a recording wire, placed 4 mm posterior to Bregma and 1 mm lateral to midline. Acrylic dental cement (A–M Systems, Carlsborg, WA) was used to firmly attach the wires and anchor screws to the skull. After the cement dried, the incision was closed around the head plug. Rats were removed from the stereotaxic holder and allowed to fully recover on a heating pad before being placed in their home cages. The head plug was left available for attachment of the preamplifier cable for EEG recordings.

Startle / ERP testing apparatus: A single startle chamber (SR-LAB, San Diego Instruments, San Diego, CA) was housed in a sound-attenuated room with a 60 dB(A) ambient noise level, and consisted of a Plexiglas cylinder 8.2 cm in diameter resting on a 12.5 × 25.5 cm Plexiglas frame within a ventilated enclosure. The cylinder was modified with an elevated roof that allowed animals to move freely despite the presence of an EEG headpiece. The test chamber was also modified with electrical insulation and an electrical interface cable that fastened to the EEG headpiece. Noise bursts were presented via a speaker mounted 24 cm above the cylinder. A piezoelectric accelerometer mounted below the Plexiglas frame detected and transduced motion within the cylinder. Stimulus delivery was controlled by the SR-LAB microcomputer and interface assembly that also digitized (0–4095), rectified and recorded stabilimeter readings, with 100 1-ms readings collected beginning at stimulus onset. Startle amplitude was defined as the average of the 100 readings. Background noise and all acoustic stimuli were delivered through one Radio Shack Supertweeter (frequency response predominantly between 5 and 16 kHz). Other methodological details are found in published materials [16].

EEG signals were recorded via a preamplifier cable connection from the rat to an A–M Systems 2 Channel Microelectrode AC Amplifier (Carlsborg, WA, Model 1800). The recording cable contained three male pins at the proximal end, which connected to the preamplifier, and three male amphenol pins at the distal end of the cable, to connect with the female pins in the head plug. The filter settings on the amplifier were 0.1 Hz low cut-off and 500 Hz high cut-off. Notch filter was in “Out” position; mode was set for record, and gain was set at 10K. The amplified signals were recorded on the SR-LAB microcomputer.

Contemporaneous startle / ERP testing: Approximately 7 days post-surgery, rats were acclimated to a test cylinder for 30 min 1 day prior to a matching session. The matching session is 10 min long and consists of a 5 min, 70 dB background, acclimation period followed by 1 block of 2 startle trial types: PULSE trials (120 dB noise bursts) and PREPULSE trials (20 ms noise bursts 12 dB over background followed 100 ms by a PULSE). Startle/ERP testing began 2 days later without drug injection, to demonstrate functionality of the ERP electrodes, and to assess baseline levels of PPI and N40 gating. Drug testing began 2 – 4 days later.

For testing, rats were brought to the laboratory in their home cages, weighed, and placed in individual cages. Test sessions were approximately 35 min long and consisted of a 5 min, 65 dB background, acclimation period followed by 5 startle trial types: PULSE trials (120 dB noise bursts), PREPULSE trials (20 ms noise bursts 70, 75 or 80 dB followed 100 ms by a PULSE) and NOSTIM trials (stabilimeter recordings obtained when no stimulus was presented). The session also included 60 N40 click pairs: 1 ms 85 dB(A) white noise, separated by 500 ms with a fixed intertrial interval of 15 sec. The session consisted of initial (block 1) and final (block 6) blocks of 5 PULSE trials, separated by 2 blocks of 30 click pairs (blocks 2 and 5) and 2 blocks that included 5 PULSE trials and 15 PREPULSE trials (the latter divided equally among 70, 75 and 80 dB prepulse intensities) (blocks 3 and 4). NOSTIM trials were interspersed between startle and PPI trials which were used to assess gross motor activity during the test session, but were not included in the calculation of intertrial intervals, which were

variable and averaged 15 s. Reflex habituation was determined based on the change in startle magnitude from the initial to the final block of PULSE trials; this measure detected no meaningful differences and is thus not reported.

ERP signal processing: EEG processing was performed offline using Neuroscan Reader Station v4.3.1 (Compumedics, El Paso, TX). Individual EEG responses to each click pair were high pass filtered (1 Hz; 12db/octave rolloff), baseline corrected across the entire sweep, and manually screened for amplifier saturation or other artifacts. Waveform averaging was performed on artifact-free EEG epochs. The resultant averaged evoked potential waveforms were baseline corrected (0–10 ms). The N40 component was calculated for averaged responses to the first (S1) and second (S2) clicks as the maximum negative waveform in the 20–60 ms range relative to the P20 component, which was defined as the positive component that preceded the N40 or the maximum positive voltage in the 0–30 ms range. N40 gating was calculated as $N40-P20\ S2/N40-P20\ S1$.

PPI and EEG were acquired on 5 days - once drug-free, and then on 4 days after treatment with APO (apomorphine hydrochloride hemihydrate, sc; Sigma) or vehicle (0.01% Ascorbic Acid, sc; Sigma) in a balanced within-subject design. APO was diluted in 0.01% Ascorbic Acid and was administered immediately prior to testing. APO dose (0, 0.1, 0.25, 0.5 mg/kg) was calculated as mg/kg of salt. All tests were separated by 3–4 days, and drug order balanced across groups based on average PPI levels during the matching session.

Statistics

1. Startle / PPI: Prepulse inhibition was defined as $100 - [(startle\ amplitude\ on\ prepulse + pulse\ trials / startle\ amplitude\ on\ PULSE\ trials) \times 100]$, and was analyzed by mixed-design analyses of variance (ANOVAs), with specific comparisons noted for each experiment. ANOVAs were also used to assess startle magnitude on PULSE trials during PPI testing.
2. N40 ERP gating: N40 amplitudes were analyzed by ANOVA, with trial (S1, S2) as a within-subject factor and dose as a within-subject factor. S2/S1 ratios were compared by repeated measure ANOVA. At baseline (no drug) testing, 5 / 57 (8.8%) of the rats exhibited no detectable S1 signal, and were excluded from analyses of gating ratios. Similarly, in drug testing, rats with no measurable S1 were excluded from analyses of gating ratios; for rats with measurable S1 responses but no S2 response, S2 values of -0.001 were substituted for ratio calculations.

Alpha was 0.05 for all statistical analyses.

Results

Baseline Testing

Baseline (drug-free) measures revealed no group difference in startle magnitude in LE vs. SD rats ($F < 1$) (Figure 1A, inset). PPI was significantly lower in LE vs. SD rats: ANOVA revealed significant main effects of strain ($F=11.69$, $df\ 1,55$, $p<0.0012$) and prepulse intensity ($F=25.47$, $df\ 2,110$, $p<0.0001$), but no strain $\times$ intensity interaction ($F=0.83$, $df\ 2,110$, ns) (Figure 1A). Mean %PPI (SEM) across all intensities was 52.20 (1.68)% in SD vs. 38.80 (1.77)% in LE rats.

N40 amplitude and gating did not differ significantly between strains. Analysis of N40 amplitude revealed no main effects of strain ($F<1$), a main effect of stimulus order ($S1 > S2$) ($F=129.29$, $df\ 1,50$, $p<0.0001$), and no strain $\times$ stimulus order interaction, though a trend was noted ($F=2.84$, $df\ 1,50$, $p < 0.10$) (Figure 1B, inset). Similarly, strain differences in gating ratios

in SD vs. LE rats approached significance (0.45 (0.034 (SEM)) vs. 0.57 (0.053); $F=3.62$, df 1,50, $p < 0.065$) (Figure 1B). Neither S1 amplitudes nor N40 gating ratios correlated significantly with startle magnitude (R 's = 0.12 and 0.14, respectively) or PPI (R 's = -0.14 and -0.18, respectively).

Apomorphine dose-response testing

As previously reported, APO reduced startle magnitude on pulse alone trials; here this effect exhibited a U-shaped dose function (Figure 3A, inset). ANOVA of startle magnitude on pulse alone trials revealed a near-significant effect of strain ($F=3.90$, df 1,52, $p<0.06$), and a significant effect of APO dose ($F=3.66$, df 3,156, $p<0.015$), but no significant strain $\times$ dose interaction ($F<1$). Post-hoc comparisons revealed that, compared to post-vehicle levels, startle magnitude was reduced after 0.1 mg/kg APO ($p<0.03$) and 0.25 mg/kg APO ($p<0.002$), but not after 0.5 mg/kg APO (NS).

APO reduced PPI in both rat strains (Figure 3A). ANOVA of PPI revealed no significant main effect of strain ($F<1$), but significant effects of APO dose ($F=38.68$, df 3,156, $p<0.0001$) and prepulse intensity ($F=19.10$, df 2,104, $p<0.0001$), and significant interactions of dose $\times$ strain ($F=6.39$, df 3,156, $p<0.0004$) and dose $\times$ intensity ($F=7.29$, df 6,312, $p<0.0001$). The dose $\times$ strain interaction reflected the fact that PPI in LE rats was significantly lower than in SD rats after vehicle ($F=5.41$, df 1,52, $p<0.025$), but not after 0.1 or 0.25 mg/kg APO (ns); furthermore, after 0.5 mg/kg APO, PPI was actually significantly elevated in LE vs. SD rats ($F=9.14$, df 1,52, $p<0.004$). This pattern reflected the linear dose-dependent PPI-disruptive effects of APO in SD rats, but the lack of dose-sensitivity in LE rats. We have previously reported this differential strain pattern after both systemic and intracerebral administration of DA agonists in SD vs. LE rats [43].

The effects of APO on startle magnitude and PPI were easily dissociated in these data: APO effects on startle magnitude could account for neither the PPI-reducing effects of APO nor the differential strain sensitivity to these effects. For example, in SD rats, the lowest dose of APO (0.1 mg/kg) produced the greatest reduction in startle magnitude but the least reduction in PPI; in contrast, the highest dose of APO (0.5 mg/kg) did not significantly reduce startle magnitude yet produced the most robust disruption of PPI. Among subgroups of vehicle vs. APO dose groups matched for startle magnitude, ANOVA of PPI reproduced the findings of the inclusive sample of rats: no significant effect of strain ($F<1$), a significant effect of APO dose ($F=29.13$, df 3,138, $p<0.0001$), and a significant interaction of APO dose $\times$ strain ($F=3.40$, df 3,138, $p<0.02$), confirming SD $>$ LE sensitivity to the PPI-disruptive effects of APO, independent of startle magnitude.

As in drug-free startle testing, levels of N40 gating after vehicle did not differ significantly between SD and LE rats, with S2/S1 ratios suggesting only a modest trend towards higher gating in SD rats ($F=2.59$, df 1,46, ns; Figure 3B). APO significantly disrupted N40 gating and reduced S1 amplitude in SD and LE rats (Figure 3B, inset). APO also caused a dose-dependent increase in the S2/S1 "gating" ratio in SD, while this increase in LE rats reached maximal levels (approximately 1.0) with all active doses of APO (Figure 3B). After excluding rats with no measurable S1 amplitude, ANOVA of S2/S1 ratios revealed significant effects of APO dose ($F=3.15$, df 3,111, $p<0.03$), and no significant main effect of strain ($F=1.01$, df 1,37, ns) or strain $\times$ APO interaction ($F=1.05$, df 3, 111, ns). ANOVA of N40 amplitude (Figure 3B, inset) revealed a significant main effect of stimulus order ($F=50.95$, df 1,111, $p<0.0001$) ($S1 > S2$) and APO dose ($F=22.04$, df 3,111, $p<0.0001$), but no significant main effects of strain ($F<1$). There was a significant interaction of APO $\times$ stimulus order ($F=17.16$, df 3,111, $p<0.0001$), but not APO $\times$ strain or APO $\times$ strain $\times$ stimulus order. Inspection of the data revealed that APO reduced S1 amplitude disproportionately to S2 amplitude in both strains (but increased S2 amplitude in neither strain), suggestive of reduced stimulus registration; the failure of APO

to increase S2 amplitude suggests no reduction in "gating" per se. ANOVA of S1 amplitude, excluding rats with unmeasurable S1 values, revealed a significant main effect of APO dose ($F=25.89$, $df\ 3,111$, $p<0.0001$), no significant effect of strain ($F<1$) and no significant dose $\times$ strain interaction ($F=1.22$, $df\ 3,111$, ns). These results were not substantively different when all rats (i.e. even those without measurable S1 amplitudes, coded as "-0.001") were included in the analyses.

APO effects on the primary startle and ERP gating variables were compared. A measure of APO sensitivity, or "APO effect" [46], was calculated as the arithmetic difference between vehicle and active dose conditions for PPI, startle magnitude, N40 gating and S1 amplitude. Regression analyses revealed no significant correlations between APO effects on startle amplitude and S1 amplitude ($R=0.23$, ns) or S2/S1 ratios ($R=-0.18$, ns), or between PPI and S1 amplitude ($R=0.01$, ns) or S2/S1 ratio ($R=0.11$, ns).

Discussion

These studies demonstrate rat strain difference in the DAergic regulation of sensorimotor gating (PPI) but not sensory gating (S2/S1 ratio) or sensory registration (S1 amplitude). The observed differences in PPI sensitivity were independent of APO-induced changes in startle magnitude. In both SD and LE rats, APO-induced increases in S2/S1 ratios reflected drug effects on S1 amplitude. A link between reduced ERP suppression and diminished responsivity to S1 stimuli has been reported previously in both preclinical [2,10–12,31–33] and clinical studies [2,4,14,22,23].

The literature is replete with strain differences in complex phenotypes. The distinction of the phenotypes reported here - PPI and ERP-based sensory gating - relates not only to the fact that they are schizophrenia endophenotypes, but also to the fact that we understand a significant amount about their underlying neurobiology. For example, PPI APO sensitivity in rats is associated with specific heritable neurobiological mechanisms, including differences within D2-linked signal transduction pathways in the nucleus accumbens [27,28,39], and with the differential expression of specific accumbens genes [30]. Some of these same genes have been implicated in the regulation of PPI in humans (e.g. catechol-O-methyl transferase: Roussos [26]). While much is known about the cellular and neurochemical substrates regulating ERP gating [3,11,12,19,21,32–35,38], we do not yet know whether APO effects on N40 gating and PPI are related to the same accumbens intracellular and genetic substrates.

While reduced inhibition in PPI and ERP gating in schizophrenia may reflect somewhat overlapping information-processing or "gating" abnormalities, there is also significant divergence in the demographic, symptom, neurocognitive, and functional correlates of these measures, as well as separable and distinct neurobiological substrates, and probably different genetic architectures [7,11–13,18,²⁰,24,29,37,40]. Our studies in large schizophrenia and normal comparison cohorts suggest that while the positive correlation of PPI and P50 gating reaches statistical significance, it does so only in normal comparison subjects, with a correlation ($r = 0.33$) that accounts for only 10% of the variance in these measures. It is thus not surprising that PPI and N40 gating in the present study were not significantly correlated during baseline testing [40].

However, based on the fact that PPI, N40 "gating" and S1 amplitude were all impaired by APO, it was striking that the *APO sensitivities* of these measures were not significantly correlated. One interpretation of these results is that different neural substrates regulate the APO effects on PPI and N40 gating and registration. For example, while the PPI-disruptive effects of APO may be regulated by ventral forebrain structures including the NAC and descending polysynaptic projections to the pons (cf. [37]), the dopaminergic regulation of N40 gating and

registration may be mediated in part or predominantly via "feed-forward" interactions between the NAC and both cortex and thalamus [11]. Within any given rat, the sensitivities of these different substrates might easily be independent of each other. This independence might reflect the fact that the distinct pathways to either measure ("downstream" for PPI and "upstream" for N40 gating and registration) introduce different influences that dilute the impact of a common element (e.g. accumbens D2 receptor sensitivity).

The link between reduced ERP suppression and diminished responsivity to S1 stimuli – detected here as a significant drug effect on both measures - has been reported previously in both [2,10–12,32,33]; and clinical studies [1,4,14,,22,23]. In clinical studies, reduced S1 magnitude often contributes to an increase in S2/S1 ratio in schizophrenia groups, even to a greater degree than does an absolute increase in S2 magnitude. Conceivably, diminished early sensory registration suggested by reduced S1 ERP magnitude in schizophrenia, and in preclinical models, might reflect genetic and neural events of direct relevance to the pathophysiology of this disorder. Here, we report that LE and SD rats comparatively sensitive to the S1-reducing effects of APO. Because there are known differences in DA-linked gene expression between these strains [30], it may be very feasible to identify genes that contribute to the DAergic regulation of S1 responsivity. Such genes would then be strong candidates for association with schizophrenia-linked deficits in early sensory registration.

While there were no significant strain differences in absolute S1 APO sensitivity per se, the present data suggest distinct patterns of APO dose effects across strains on S1 amplitude: after APO, SD rats exhibited a linear dose-dependent decrease in S1 amplitude, while LE rats exhibited maximal effects at the lowest APO dose, that was sustained at higher doses. Indeed, in sharp contrast to strain patterns with PPI, these different dose-response patterns with S1 amplitude might suggest greater sensitivity in LE rats, at least at the lowest APO doses.

In the present study, we observed reduced baseline and post-vehicle PPI in LE vs. SD rats. We have previously detected this difference only in studies that involved physical restraint of LE rats for intracerebral injections (even if no injection was given) [43]. While no such restraint was used in the present study, the fact that rats were connected by their head plug to a cable during testing clearly imposed some degree of physical restraint. Absent such restraints, we have detected no strain differences in baseline or post-vehicle acoustic PPI between SD and LE rats [30,38,39,41–47]. Conceivably, LE rats - - though less sensitive than SD's to the PPI-disruptive effects of DA agonists -- are more sensitive to the effects of stress on PPI. PPI appeared more sensitive in detecting these differences, as baseline and post-vehicle showed only non-significant trends towards reductions in LE vs. SD rats.

In summary, the present report: 1) replicates a reported strain difference in PPI APO sensitivity, 2) demonstrates no strain difference in N40 gating, 3) clarifies that APO effects on S2/S1 ratios largely reflect differences in S1 ERP APO sensitivity, and 4) that PPI and ERP APO sensitivity do correlate within the same rats. In total, these findings extend our understanding of an existing model for heritable gating differences in PPI "disruptability", and identify a potentially new model for understanding the neurobiology and genetics of clinical differences in sensory registration, measured by S1 amplitude.

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References

1. Adler LE, Pachtman E, Franks RD, Pecevich M, Waldo MC, Freedman R. Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. *Biol Psychiatry* 1982;17:639–654. [PubMed: 7104417]
2. Adler LE, Rose G, Freedman R. Neurophysiological studies of sensory gating in rats: effects of amphetamine, phencyclidine, and haloperidol. *Biol Psychiatry* 1986;21:787–798. [PubMed: 3730461]
3. Boutros NN, Uretsky N, Berntson G, Bornstein R. Effects of cocaine on sensory inhibition in rats: Preliminary data. *Biol Psychiatry* 1994;36:242–248. [PubMed: 7986889]
4. Boutros NN, Zouridakis G, Overall J. Replication and extension of P50 findings in schizophrenia. *Clin Electroencephalogr* 1991;22:40–45. [PubMed: 1991411]
5. Braff, DL.; Freedman, R. *Neuropsychopharmacology: The Fifth Generation of Progress*. Baltimore MD: Lippincott Williams & Wilkins; 2002. The importance of endophenotypes in studies of the genetics of schizophrenia; p. 703-716.
6. Braff D, Stone C, Callaway E, Geyer M, Glick I, Bali L. Prestimulus effects on human startle reflex in normals and schizophrenics. *Psychophysiology* 1978;14:339–343. [PubMed: 693742]
7. Brenner CA, Edwards CR, Carroll CA, Kieffaber PD, Hetrick WP. P50 and acoustic startle gating are not related in healthy participants. *Psychophysiology* 2004;41:702–708. [PubMed: 15318876]
8. Calkins ME, Dobie DJ, Cadenhead KS, Olincy A, Freedman R, Green MF, Greenwood TA, Gur RE, Gur RC, Light GA, Mintz J, Nuechterlein KH, Radant AD, Schork NJ, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Braff DL. The consortium on the genetics of endophenotypes in schizophrenia (COGS): model recruitment, assessment and endophenotyping methods for a multi-site collaboration. *Schizophr Bull* 2007;33:33–48. [PubMed: 17035358]
9. Connolly PM, Maxwell C, Liang Y, Kahn JB, Kanes SJ, Abel T, Gur RE, Turetsky BI, Siegel SJ. The effects of ketamine vary among inbred mouse strains and mimic schizophrenia for the P80, but not P20 or N40 auditory ERP components. *Neurochem Res* 2004;29:1179–1188. [PubMed: 15176475]
10. de Bruin NM, Ellenbroek BA, Cools AR, Coenen AM, van Lijstelaar EL. Differential effects of ketamine on gating of auditory evoked potentials and prepulse inhibition in rats. *Psychopharmacology* 1999;142:9–17. [PubMed: 10102777]
11. de Bruin NM, Ellenbroek BA, van Lijstelaar EL, Cools AR, Stevens KE. Hippocampal and cortical sensory gating in rats: Effects of quinpirole microinjections in nucleus accumbens core and shell. *Neuroscience* 2001a;105:169–180. [PubMed: 11483310]
12. de Bruin NM, van Lijstelaar EL, Cools AR, Ellenbroek BA. Auditory information processing in rat genotypes with different dopaminergic properties. *Psychopharmacology* 2001b;156:352–359. [PubMed: 11549235]
13. Ellenbroek BA, van Lijstelaar G, Frenken M, Cools AR. Sensory gating in rats: Lack of correlation between auditory evoked potential gating and prepulse inhibition. *Schizophr Bull* 1999;25:777–788. [PubMed: 10667747]
14. Freedman R, Adler LE, Waldo MC, Pachtman E, Franks RD. Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: comparison of medicated and drug-free patients. *Biol Psychiatry* 1983;18:537–551. [PubMed: 6134559]
15. Freedman R, Coon H, Myles-Worsley M, Orr-Urtreger A, Olincy A, Davis A, Polymeropoulos M, Holik J, Hopkins J, Hoff M, Rosenthal J, Waldo MC, Reimherr F, Wender P, Yaw J, Young DA, Breese CR, Adams C, Patterson D, Adler LE, Kruglyak L, Leonard S, Byerley W. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. *Proc Natl Acad Sci USA* 1997;94:587–592. [PubMed: 9012828]
16. Geyer, MA.; Swerdlow, NR. The startle reflex and its use in preclinical measures of sensorimotor gating. In: Crawley, JN.; Skolnick, P., editors. *Current Protocols in Neuroscience*. New York: John Wiley & Sons; 1998. p. 8.7.1-8.7.15.
17. Greenwood TA, Braff DL, Light GA, Cadenhead KS, Calkins ME, Dobie DJ, Freedman R, Green MF, Gur RE, Gur RC, Mintz J, Nuechterlein KH, Olincy A, Radant AD, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Schork NJ. Initial

- heritability analyses of endophenotypic measures for schizophrenia: the Consortium on the Genetics of Schizophrenia (COGS). *Arch Gen Psychiatry* 2007;64:1242–1250. [PubMed: 17984393]
18. Grunwald T, Boutros NN, Pezer N, von Oertzen J, Fernandez G, Schaller C, Elger CE. Neuronal substrates of sensory gating within the human brain. *Biol Psychiatry* 2003;53:511–519. [PubMed: 12644356]
 19. Halene TB, Siegel SJ. Antipsychotic-like properties phosphodiesterase 4 inhibitors: evaluation of 4-(3-butoxy-4-methoxybenzyl)-2-imidazolidinone (RO-20-1724) with auditory event-related potentials and prepulse inhibition of startle. *J Pharmacol Exp Ther* 2008;326:230–239. [PubMed: 18420599]
 20. Light GA, Braff DL. Measuring P50 suppression and prepulse inhibition in a single recording session. *Am J Psychiatry* 2001;158:2066–2068. [PubMed: 11729028]
 21. Maxwell CR, Liang Y, Kelly MP, Kanes SJ, Abel T, Siegel SJ. Mice expressing constitutively active G α exhibit stimulus encoding deficits similar to those observed in schizophrenia patients. *Neuroscience* 2006;141:1257–1264. [PubMed: 16750890]
 22. Myles-Worsley M. P50 sensory gating in multiplex schizophrenia families from a Pacific island isolate. *Am J Psychiatry* 2002;159:2007–2012. [PubMed: 12450949]
 23. Nagamoto HT, Adler LE, Waldo MC, Freedman R. Sensory gating in schizophrenics and normal controls: Effects of changing stimulation interval. *Biol Psychiatry* 1989;25:549–561. [PubMed: 2920190]
 24. Oranje B, van Berckel BN, Kemmer C, van Ree JM, Kahn RS, Verbaten MN. P50 suppression and prepulse inhibition of the startle reflex in humans: a correlational study. *Biol Psychiatry* 1999;45:883–890. [PubMed: 10202576]
 25. Palmer AA, Dulawa SC, Mottiwala AA, Conti LH, Geyer MA, Printz MP. Prepulse startle deficit in the Brown Norway rat: a potential genetic model. *Behav Neurosci* 2000;114:374–388. [PubMed: 10832798]
 26. Roussos P, Giakoumaki SG, Rogdaki M, Pavlakis S, Frangou S, Bitsios P. Prepulse inhibition of the startle reflex depends on the catechol O-methyltransferase Val158Met gene polymorphism. *Psychol Med*. 2008 [Epub ahead of print Feb 8, 2008].
 27. Saint Marie RL, Neary AC, Shoemaker JM, Swerdlow NR. The effects of apomorphine and d-amphetamine on striatal c-Fos expression in Sprague-Dawley and Long Evans rats and their F1 progeny. *Brain Res* 2006;1119:203–214. [PubMed: 16979142]
 28. Saint Marie RL, Neary AC, Shoemaker JM, Swerdlow NR. Apomorphine effects on CREB phosphorylation in the nucleus accumbens of rat strains that differ in PPI sensitivity. *Biol Psychiatry* 2007;61:37S.
 29. Schwarzkopf SB, Lamberti JS, Smith DA. Concurrent assessment of acoustic startle and auditory P50 evoked potential measures of sensory inhibition. *Biol Psychiatry* 1993;33:815–828. [PubMed: 8373920]
 30. Shilling PD, Saint Marie RL, Shoemaker JM, Swerdlow NR. Strain differences in the gating-disruptive effects of apomorphine: Relationship to gene expression in nucleus accumbens signaling pathways. *Biol Psychiatry* 2008;63:748–758. [PubMed: 18083141]
 31. Siegel SJ, Maxwell CR, Majumdar S, Trief DF, Lerman C, Gur RE, Kanes SJ, Liang Y. Monoamine reuptake inhibition and nicotine receptor antagonism reduce amplitude and gating of auditory evoked potentials. *Neuroscience* 2005;133:729–738. [PubMed: 15908134]
 32. Stevens KE, Fuller LL, Rose GM. Dopaminergic and noradrenergic modulation of amphetamine-induced changes in auditory gating. *Brain Res* 1991;555:91–98. [PubMed: 1681997]
 33. Stevens KE, Luthman J, Lindqvist E, Johnson RG, Rose GM. Effects of neonatal dopamine depletion on sensory inhibition in the rat. *Pharmacol Biochem Behav* 1996;53:817–823. [PubMed: 8801583]
 34. Stevens KE, Meltzer J, Rose GM. Disruption of sensory gating by the α 2 selective noradrenergic antagonist yohimbine. *Biol Psychiatry* 1993;33:130–132. [PubMed: 8439602]
 35. Stevens KE, Meltzer J, Rose GM. Nicotinic cholinergic normalization of amphetamine-induced loss of auditory gating in freely moving rats. *Psychopharmacology* 1995;119:163–170. [PubMed: 7659763]

36. Swerdlow NR, Breier M, Mora AB, Ko D, Shoemaker JM. A novel rat strain with enhanced sensitivity to the effects of dopamine agonists on startle gating. *Pharmacol Biochem Behav* 2008a;88:280–290. [PubMed: 17936348]
37. Swerdlow NR, Geyer MA, Braff DL. Neural circuitry of prepulse inhibition of startle in the rat: Current knowledge and future challenges. *Psychopharmacology* 2001a;156:194–215. [PubMed: 11549223]
38. Swerdlow NR, Geyer MA, Shoemaker JM, Light GA, Braff DL, Stevens KE, Sharp R, Breier M, Neary A. Convergence and divergence in the neurochemical regulation of prepulse inhibition of startle and N40 suppression in rats. *Neuropsychopharmacology* 2006a;31:506–515. [PubMed: 16123772]
39. Swerdlow NR, Krupin AS, Bongiovanni MJ, Shoemaker JM, Goins JC, Hammer RP Jr. Heritable differences in the dopaminergic regulation of behavior in rats: Relationship to D2-like receptor G protein function. *Neuropsychopharmacology* 2006b;31:721–729. [PubMed: 16123742]
40. Swerdlow NR, Light GA, Cadenhead KC, Sprock J, Hsieh MH, Braff DL. Startle gating deficits in a large cohort of patients with schizophrenia: Relationship to medications, symptoms, neurocognition and level of function. *Arch Gen Psychiatry* 2006c;63:1325–1335. [PubMed: 17146007]
41. Swerdlow NR, Platten A, Kim YK, Gaudet I, Shoemaker J, Pitcher L, Auerbach P. Sensitivity to the dopaminergic regulation of prepulse inhibition in rats: Evidence for genetic, but not environmental determinants. *Pharmacol Biochem Behav* 2001b;70:219–226. [PubMed: 11701191]
42. Swerdlow NR, Shoemaker JM, Auerbach PP, Pitcher L, Goins J, Platten A. Heritable differences in the dopaminergic regulation of sensorimotor gating: II. Temporal, pharmacologic and generational analyses of apomorphine effects on prepulse inhibition. *Psychopharmacology* 2004b;174:452–462. [PubMed: 15300359]
43. Swerdlow NR, Shoemaker JM, Bongiovanni M, Neary A, Tochen L, Saint Marie RL. Strain differences in the disruption of prepulse inhibition of startle after systemic and intra-accumbens amphetamine administration. *Pharmacol Biochem Behav* 2007;87:1–10. [PubMed: 17475315]
44. Swerdlow NR, Shoemaker JM, Crain S, Goins J, Onozuka K, Auerbach PP. Sensitivity to drug effects on prepulse inhibition in inbred and outbred rat strains. *Pharmacol Biochem Behav* 2004c;77:291–302. [PubMed: 14751457]
45. Swerdlow NR, Shoemaker JM, Pitcher L, Platten A, Kuczenski R, Eleey CC, Auerbach P. Genetic differences in startle gating-disruptive effects of apomorphine: evidence for central mediation. *Behavioral Neuroscience* 2002;116:682–690. [PubMed: 12148935]
46. Swerdlow NR, Shoemaker JM, Platten A, Pitcher L, Goins J, Auerbach PP. Heritable differences in the dopaminergic regulation of sensorimotor gating. I. Apomorphine effects on startle gating in albino and hooded outbred rat strains and their F1 and N2 progeny. *Psychopharmacology* 2004a;174:441–451. [PubMed: 15300358]
47. Swerdlow NR, Shoemaker JM, Platten A, Pitcher L, Goins J, Crain S. Heritable differences in the effects of amphetamine but not DOI on startle gating in albino and hooded outbred rat strains. *Pharmacol Biochem Behav* 2003;75:191–197. [PubMed: 12759127]
48. Swerdlow NR, Weber M, Qu Y, Light GA, Braff DL. Realistic expectations of prepulse inhibition in translational models for schizophrenia research. *Psychopharmacology* 2008b;199:331–388. [PubMed: 18568339]
49. Turetsky BI, Calkins ME, Light GA, Olincy A, Radant AD, Swerdlow NR. Neurophysiological endophenotypes of schizophrenia: The viability of selected candidate measures. *Schizophr Bull* 2007;33:69–94. [PubMed: 17135482]

Figure 1.

Startle (A) and ERP (B) measures in SD and LE rats during drug-free test session. A. Significant strain difference in PPI (SD > LE; ** $p < 0.0012$) but not startle magnitude (inset). B. Near-significant difference in N40 gating ratio (SD > LE; $p < 0.065$) but not S1 or S2 amplitude (inset).

Figure 2. Grand average N40 ERP waveforms in SD and LE rats during drug-free test session, showing responses to S1 and "gated" S2 stimuli.

Figure 3.

Startle (A) and ERP (B) measures in SD and LE rats during APO dose-response testing. A. Significant strain differences in post-vehicle levels of PPI (SD > LE (*)) and post-APO levels of PPI (LE > SD (#)) but not startle magnitude (inset). B. N40 gating ratio significantly increased by APO in both SD and LE strains, with no significant difference in either post-vehicle or post-APO levels of N40 gating. Inset shows APO-suppression of S1 amplitude in both SD and LE rats, with no strain differences in APO sensitivity. * $p < 0.015$; ** $p < 0.008$ vs vehicle, collapsed across strains.

Figure 4. Grand average N40 ERP waveforms in SD and LE rats during APO dose-response testing. Note progressive loss of S1 amplitude with increasing APO dose in both strains.