Research report

Inhibition of auditory evoked potentials and prepulse inhibition of startle in DBA/2J and DBA/2Hsd inbred mouse substrains

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Abstract

Previous data have shown differences among inbred mouse strains in sensory gating of auditory evoked potentials, prepulse inhibition (PPI) of startle, and startle amplitude. These measures of sensory and sensorimotor gating have both been proposed as models for genetic determinants of sensory processing abnormalities in patients with schizophrenia and their first-degree relatives. Data from our laboratory suggest that auditory evoked potentials of DBA/2J mice differ from those previously described for DBA/2Hsd. Therefore, we compared evoked potentials and PPI in these two closely related substrains based on the hypothesis that any observed endophenotypic differences are more likely to distinguish relevant from incidental genetic heterogeneity than similar approaches using inbred strains that vary across the entire genome. We found that DBA/2Hsd substrain exhibited reduced inhibition of evoked potentials and reduced startle relative to the DBA/2J substrain without alterations in auditory sensitivity, amplitude of evoked potentials or PPI of startle. These results suggest that gating of auditory evoked potentials and PPI of startle measure different aspects of neuronal function. The differences between the substrains might reflect genetic drift. Alternatively, differences could arise from different rearing environments or other non-genetic factors. Future studies will attempt to determine the cause of these differences in sensory and sensorimotor processing between these two closely related inbred mouse strains.
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1. Introduction

Many patients with schizophrenia and approximately half of their family members demonstrate decreased ability to inhibit either startle or auditory evoked potentials following repeated stimuli [3,6,24,67,78]. These deficits have been interpreted as evidence for neuronal abnormalities in the circuits involved in auditory stimulus processing and/or motor responses. The observation that deficits in the inhibition of evoked potentials and startle are present in half of

first-degree relatives of patients with schizophrenia has been seen as evidence for genetic transmission of this phenotype [9,43,67]. Therefore, a great deal of effort has been invested in creating animal models that recreate the genetic and neuronal factors underlying gating abnormalities [4,8,10,17,22,24,28,29,31,37,39,40,45,47–49,54,55, 59,73,74,79,96]. DBA/2 inbred mice have been proposed as one such model that mimics several endophenotypes of schizophrenia, including prepulse inhibition (PPI) of startle, inhibition of auditory evoked potentials, and more recently novelty detection using auditory evoked potentials [14,16,43,54,55,68,70–73,76].

Both sensory and sensorimotor gating deficits have been studied in animals by measuring the reduction in startle reflexes or the inhibition of auditory evoked potentials following repeated stimuli. Previous studies have shown differences among inbred mouse strains in sensory gating of

auditory evoked potentials and prepulse inhibition of startle [7,14,55,74]. These measures of sensory and sensorimotor gating have been proposed as models of genetic determinants of sensory processing abnormalities in patients with schizophrenia and their first-degree relatives [8,67,78]. Although the inhibition of evoked potentials and PPI of startle measure different aspects of sensory processing, DBA/2 mice have been identified as one strain that exhibit impairments in both tasks, suggesting that it shares some relevant neurobiology with abnormal neuronal function in schizophrenia [15,17,55,73]. Preliminary data in our laboratory suggest that DBA/2J mice do not exhibit deficits in gating of evoked potentials to the degree described in previous studies of other DBA/2 substrains [68,73]. Therefore, we compared DBA/2J (Jackson Lab, Bar Harbor ME) and DBA/2Hsd (Harlan Sprague Dawley, Indianapolis, IN) substrains for both auditory evoked potentials and PPI of startle.

The neural processing of auditory information has been studied with evoked potentials in cats [13,58,63,64], mice [16,32,53,69,70,72,84,87,89], rats [15,17,72,74,75], monkeys [35,36] and humans [1,2,5,20,21,27,30,56, 57,60,61,85]. In this task, an auditory stimulus induces a progression of neural activity through successive structures in the auditory pathway such that early components (I to VI) are generated between the cochlea and medial geniculate nucleus and later components (N0, Na, Nb, N1, N2, P0, Pa, Pb, P1, P2) are generated in thalamic nuclei other than MGN, auditory cortex and association cortices [57]. The P1 and N1 components are also called the P50 and N100 in humans, reflecting their latencies at 50 and 100 ms. Corresponding P1 and N1 components in mice occur at 20 and 40 ms and are called the P20 and N40 [69,73].

Stimulus characteristics, such as interstimulus interval, can be manipulated to examine response properties in brain structures and cellular interactions that contribute to auditory processing [2,6,11,21,23,34,38,44,46,50,56,57,61,62]. These response characteristics include the amplitude and habituation of specific components and are affected by genetic, environmental and pharmacological factors. Thus, auditory evoked potentials are an ideal method to examine the interaction of genetic and pharmacological manipulations on selective aspects of neural function [2,31,67,69–73,80].

Sensory gating of evoked potentials refers to inhibition of specific components following repeated auditory stimuli, and has been particularly useful in dissecting genetic and pharmacological factors as an animal model for impaired brain function [3,15,17,31,37,72–75]. Previous studies in mice have examined two regions of the auditory ERP termed the P20 and N40 and have suggested that P20/N40 gating varies among inbred mouse strains. These studies have identified candidate genes and cellular mediators for this phenotype [43,72].

DBA/2J and DBA/2Hsd substrains diverged in 1938 when Mider sent a colony of DBA/2 mice to Sloan-

Kettering. Those mice then went to Heston at NCI, and finally to Jackson Labs in 1948 at generation 26 to become the DBA/2J strain. Another DBA/2 colony was sent from Mider to the NIH in 1951, then to The Frederick Cancer Center in 1981 at generation 135. Finally, in 1984, these mice were sent to Harlan Labs. In 1986, the DBA/2Hsd substrain was re-derived at Harlan Labs. The DBA/2J substrain was also re-derived at Jackson labs in 2002 (History kindly provided by Jackson Laboratories and Harlan Sprague Dawley). Thus, DBA/2J and DBA/2Hsd substrains have been in different rearing environments and genetically separated for 64 years. This, coupled with the recent re-derivation of both substrains, increases the likelihood that mutations now differentiate these substrains and might contribute to any observed phenotypic differences. Although previous studies have demonstrated variance among inbred strains for these two endophenotypes of schizophrenia, such studies have compared strains with variance across the entire genome for countless alleles. The current study examine two markers for impaired neuronal function, prepulse inhibition of startle and inhibition of auditory evoked potentials, in these two closely related substrains of DBA/2 inbred mice. We propose that any differences found among such closely related substrains may facilitate subsequent genetic analyses due to the greatly reduced variance across the genome, and therefore an increased likelihood that any genetic heterogeneity will be relevant to the phenotypes of interest.

2. Materials and methods

2.1. Animals

DBA/2J ($n = 17$), and DBA/2Hsd ($n = 18$) mice were obtained at 7–8 weeks of age. All testing was conducted between 8 and 10 weeks of age. Electrophysiological studies utilized 9 DBA/2J and 10 DBA/2Hsd mice for inhibition of evoked potentials ($n = 19$). Although a comprehensive review of auditory threshold in 80 inbred strains indicated that DBA/2 mice from Jackson labs hear stimuli from 56 dB, four mice from each substrain were used to demonstrate presence of acoustic brainstem responses between 58 and 80 dB at age of testing [97]. Studies of startle and prepulse inhibition used an additional 8 mice from each substrain ($n = 16$). All protocols were conducted in accordance with University Laboratory Animal Resources (ULAR) guidelines and were approved by the Institutional Animal Care and Use Committee (IACUC). Mice were housed 4–5/cage in a light- and temperature-controlled AALAC-accredited animal facility. Water and standard rodent chow were available ad lib. Experiments were conducted in The Stanley Center for Experimental Therapeutics in Psychiatry and the Center for Neurobiology and Behavior at University of Pennsylvania. All testing for evoked poten-

tials and startle/PPI was performed during the light phase between the hours of 0900 and 1300. Mice were acclimated to the housing facility for 1–2 weeks prior to behavioral testing.

3. Auditory evoked potentials

3.1. Surgery

Animals underwent stereotaxic implantation of tripolar electrode assemblies (PlasticsOne, Roanoke, VA) for non-anesthetized recording of hippocampal auditory evoked potentials. Animals were anesthetized with ketamine hydro-chloride/xylazine (100/10 mg/kg) prior to surgery. Surgical coordinates were measured relative to bregma in the x, y and z dimensions. Three stainless steel electrodes, mounted in a single pedestal, were aligned along the sagittal axis of the skull at 1 mm intervals with precut lengths of 3.0 mm (positive) and 1.0 mm (ground and negative) (Fig. 1A). Positive electrodes were placed in the CA3 hippocampal region 1.4 mm posterior, 2.75 mm lateral and 2.75 mm deep relative to bregma. Negative electrodes were placed adjacent to ipsilateral cortex at 0.6 mm anterior, 2.75 mm lateral and 0.75 mm deep relative to bregma. Ground electrodes were located between recording and reference at 0.4 mm posterior, 2.75 mm lateral and 0.75 mm deep to Bregma (Fig. 1B). The electrode pedestal was secured to skull with cyanoacrylic gel (PlasticsOne). Following surgery, animals were individually housed. To assess electrode placement following recording of evoked potentials, electrode tips were marked for histological evaluation with the Pearls iron reaction (Fig. 1C) [42].

3.2. Recording

Recording of brain activity for gating of evoked potentials was performed 7 days after implantation. Each animal was placed in a sound attenuated recording chamber (background white noise 70 dB) inside a Faraday electrical isolation cage. Electrode pedestals were connected to a 30-cm tripolar electrode cable that exited the chamber to connect to a high impedance differential AC amplifier (A-M systems, Carlsborg, WA) set to 1000 × amplification, 1 Hz/ 500 Hz band pass filter. EEG activity was recorded using ERPSYSTEM (Neurobehavioral Laboratory Software, 1991) on a 486-microprocessor computer. Each animal was allowed to explore the chamber for 15 min prior to recording to habituate to the setting. Stimuli were generated by ERPSYSTEM software and were delivered through a speaker attached to the testing chamber ceiling. Speakers were connected to a model SA-155 audio amplifier (Radio-shack, Fort Worth, TX), which was interfaced with the computer.

A series of 80 paired stimuli (1500 Hz, 10 ms duration) were presented 500 ms apart, with a 9-s inter-pair interval. A
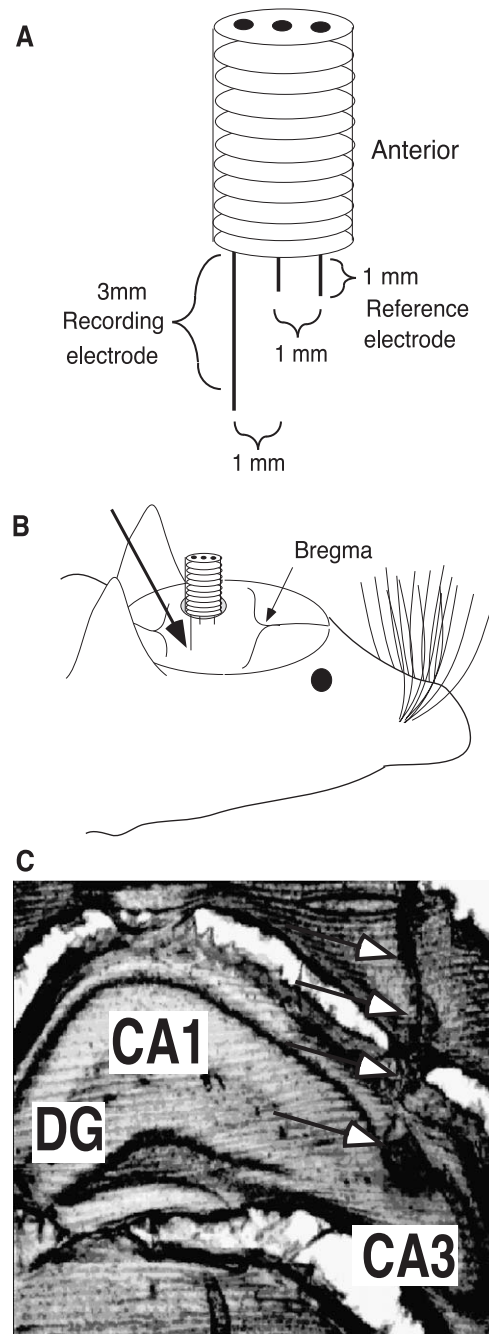

Fig. 1. (A) Representation of tripolar electrode pedestal with recording (posterior, 3 mm length), reference (anterior, 1.0 mm length) and ground (middle, 1.0 mm length) electrodes in a common base. Electrodes are separated by 1-mm intervals. The pedestal has three holes at the top to receive tripolar cable for connection to amplifier. (B) Tripolar electrode in mouse skull. Recording electrode is anterior to reference, with ground between. (C) Video micrograph of electrode placement. Lesion marks the tip of the recording electrode adjacent to the CA3 region of hippocampus. Arrows mark electrode track and lesion site. Abbreviations CA1—CA1 region of hippocampus, CA3—CA3 region of hippocampus, DG—Dentate Gyrus.

block of 80 stimulus pairs was presented at 80 dB, compared to background of 70 dB white noise. A 500 ms pre-stimulus baseline and 500 ms post stimulus were recorded

for each stimulus (sample rate 1000 Hz). Average waves were created for the response to the first and second stimulus for each mouse separately (Fig. 2A–D).

Recording for acoustic brainstem responses was performed using Spike2 software on a Pentium III microcomputer connected to a power micro 1401 II interface module (CED, Cambridge, UK) and high impedance differential AC amplifier (A-M systems) set to $1000 \times$ amplification, 1/500 Hz band pass filter. EEG activity was sampled at 6250 Hz from 2 ms prior to 10 ms after each stimulus. Stimuli consisted of a series of 1000 white noise clicks of 3 ms duration, 125 ms ISI at each intensity. The clicks were generated from 300 pips with a 10-μs duration. Stimuli were presented through speakers on the chamber ceiling (model 19-318A, 700–10,000 Hz frequency response, Radioshack) connected to a digital audio amplifier (RCA Model STAV3870 Radioshack) in 2 dB intervals from 58 dB (lowest achievable with audio amplifier on at minimum setting) to 80 dB. Additionally, ABRs were recorded with the audio amplifier turned off to create the no stimulus condition. Sound pressure level was determined using a digital sound meter placed inside each cage (set to measure the maximum sound pressure every 200 ms for frequencies between 32 and 10,000 Hz with sensitivity range between 50 and 126 dB, Radioshack). Additionally, apparatus for recording of evoked potentials and startle chambers for testing of PPI were calibrated to ensure that sound pressure levels were consistent between tasks. Electroencephalographic signal was digitally filtered between 100 and 450 Hz prior to creation of average waves. An average wave was then created for each mouse at each intensity. Fig. 3 demonstrates the grand average (A) and individual (B) ABR for each substrain ($n = 4$) in 4 dB increments from 60 to 80 dB as well as a no stimulus recording for comparison. Fig. 3C (Harlan) and E (Jackson) display the mean amplitude for the difference waveform with a positive deflection at 3 ms and a negative deflection at 5 ms. The amplitude for this component of the ABR increases with intensity between 60 and 80 dB ($F(9,63) = 2.47$, $p = 0.02$). Fig. 3D (Harlan) and F (Jackson) show decreasing latency of the positive deflection at 8 ms with increasing intensity between 60 and 80 dB ($F(9,63) = 3.17$, $p < 0.01$).

3.3. Data analysis

The amplitude of response to the P20/N40 waveform was calculated for each mouse on post-operative day 7. The P20 was measured by picking the maximum positive deflection between 10 and 30 ms. The N40 was determined by picking the most negative deflection between 25 and 60 ms. The amplitude from the peak of the P20 to the trough of the N40 was then calculated, as it is reported to be a more stable measure than either component alone and to facilitate comparison with previous literature [73]. The amplitude of response to the first and second stimuli were named A1 and A2, respectively. Additionally, the ratio of response following the second tone to the first (A2/A1) was calculated as this has been used as a measure of sensory gating in multiple previous studies [15,73–75] Repeated measures analysis of variance (ANOVA) was then used to examine the effects of strain (DBA/2J vs. DBA/2Hsd) and stimulus condition (first vs. second) on the amplitude of response for the P20/N40. Strain was designated the independent variable, with stimulus condition as a repeated measure within each mouse. Significant multivariate or interaction effects were followed by planned comparisons using Statistica 5.5 (Statsoft, Tulsa, OK) on a Pentium III personal computer. Additionally, the amplitude of response to the first stimulus
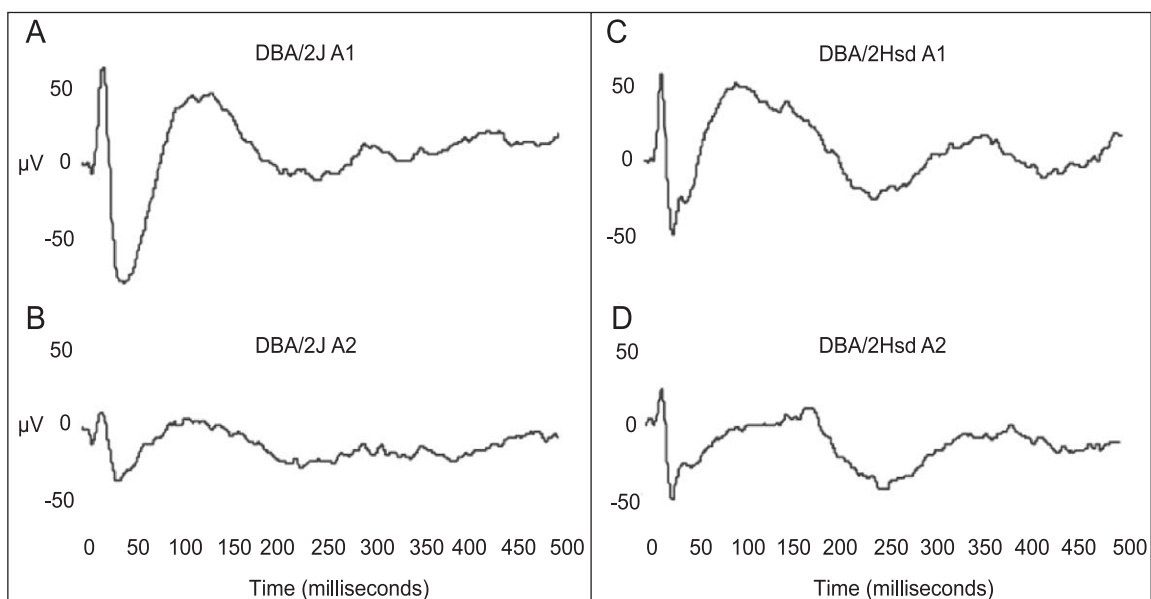

Fig. 2. Grand average of evoked potentials of both DBA/2Hsd (A, B) and DBA/2J (C, D) mice, following the first (A, C) and second (B, D) stimulus at 80 dB.
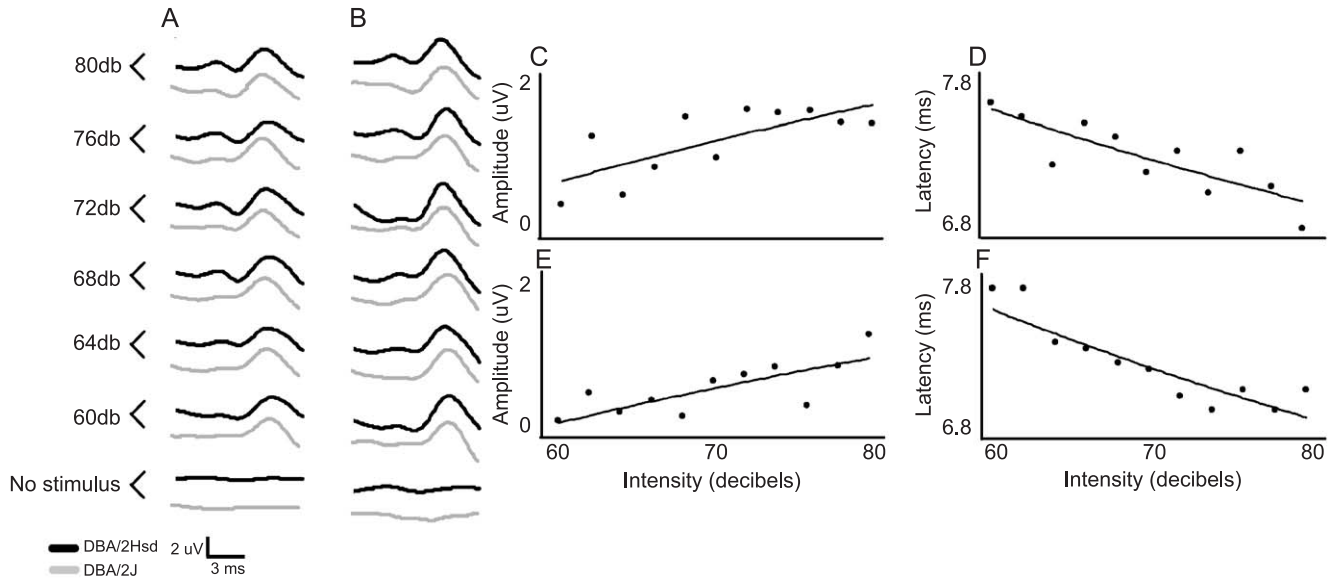
Fig. 3. Grand average (A) and individual (B) ABR for each DBA/2 substrain ($n = 4$) in 4 decibel increments from 60 to 80 dB as well as a no stimulus recording for comparison. (C) (Harlan) and (E) (Jackson) display the mean amplitude for the difference waveform with a positive deflection at 3 ms and a negative deflection at 5 ms. The amplitude for this component of the ABR increases with intensity between 60 and 80 dB ($F(9,63) = 2.47$, $p = 0.02$). (D) (Harlan) and (F) (Jackson) show decreasing latency of the positive deflection at 8 ms with increasing intensity between 60 and 80 dB ($F(9,63 = 3.17$, $p < 0.01$). Note scale bar for time in ms on the abscissa and amplitude in microvolts on the ordinate.

(A1), the amplitude of response to the second stimulus (A2) and ratio (A2/A1) were compared between strains using two-tail t-tests to assess the effects of strain on each response individually as well as to compare our results with methods used in previous studies [15,73–75].

3.4. Prepulse inhibition and startle

In the week following delivery, mice were handled and weighed daily. On test days, animals were transported to the laboratory and allowed to accommodate for at least 1 h prior to being placed in the startle apparatus (SR-Lab, San Diego Instruments, San Diego, CA). The apparatus consists of a 5.1-cm diameter Plexiglas cylinder mounted on a Plexiglas platform in a well-ventilated sound attenuated chamber. Startle stimuli are delivered by a high frequency speaker mounted 28 cm above the platform. Background noise the chamber was set at 65 dB, and response detected by a piezoelectric accelerometer mounted beneath the platform. Data were collected on a Dell 386 PC computer and subsequently processed for analysis. Startle and PPI were both collected within the same test session. Each trial started with 5 min of 70 dB background noise followed by both startle and PPI trials. Startle trials consisted of a 40 ms square-wave noise pulse at 90, 95, 100, 105, 110, 115 and 120 dB. Each stimulus was presented five times in a randomized order with an average inter-trial interval (ITI) of 15 s (range 10–20). Startle trials were followed by prepulse inhibition (PPI) trials. For these, a 40 ms prepulse was presented 80 ms prior to a 40 ms 120 dB startle stimulus. Prior studies in our laboratory indicate that these

parameters optimize PPI in DBA/2 J mice [S. Kanes, unpublished data]. PPI was recorded for prepulses of 75, 80, and 85 dB. All prepulse trials were presented five times in a randomized order with an average ITI of 15 s (range 10–20). Data were recorded as 100 1-ms voltage readings, which were averaged over the collection interval to give an average startle measure for each trial.

3.5. Data analysis

Mean values for startle and PPI {no prepulse − prepulse/ no prepulse) × 100} were subjected to one-way analysis of variance (ANOVA), with Tukey post-hoc comparison's performed where appropriate. All data was analyzed using STATA7 (Stata College Station, TX) on a Macintosh G4 personal computer.

4. Results

4.1. Auditory evoked potentials

Repeated measures ANOVA of the P20/N40 response indicates that there is no overall difference in amplitude of

Table 1

Substrain	A1 in µV	A2 in µV	Ratio in %
DBA/2Hsd	157 ± 66	95 ± 58	61 ± 26
DBA/2J	168 ± 59	58 ± 30	33 ± 10
p value	0.70	0.19	<0.01

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response between substrains at 80 dB ($F(1,17)=0.33$, $p=0.57$). DBA/2Hsd mice had amplitudes of 126 ± 68 µV (mean $\pm$ S.D.) and to DBA/2J had amplitudes of 122 ± 73 µV across both stimulus conditions. There was a main effect of stimulus condition with reduced amplitude following the second stimulus (77 ± 50 µV) relative to the first (162 ± 61 µV) across both substrains ($F(1)=63.85$, $p<0.01$). There was also an interaction of substrain and stimulus condition, indicating that the response following the first and second stimuli differed between substrains ($F(1,17)=5.15$, $p=0.04$). Planned comparison of the amplitude of response following the first stimulus indicated no difference between substrains on A1 ($t(17)=0.39$, $p=0.70$). Similarly, comparison of the amplitude of response following the second stimulus indicated no difference between substrains on A2 ($t(17)=1.3$, $p=0.19$). However, analysis for the ratio of response indicated that there is a significant difference between substrains for A2/A1 ($t(17)=2.88$, $p=0.01$) (Fig. 4 and Table 1). Thus, DBA/2Hsd display decreased inhibition of evoked potentials relative to DBA/2J mice without a significant difference in amplitude of response to the first stimulus.

4.2. Acoustic startle

There was an overall effect of substrain on acoustic startle response and significant strain by stimulus intensity interaction (Fig. 5A). DBA/2Hsd mice displayed increased startle 51.4 ± 15.3 (mean $\pm$ S.D.) relative to DBA/2J mice 20.3 ± 4.4. Substrains differed at 105 dB ($F(1,13)=10.48$, $p<0.01$), 110 dB ($F(1,13)=20.51$, $p<0.01$), 115 dB ($F(1,13)=24.15$, $p<0.01$), and 120 dB ($F(1,13)=7.71$, $p<0.02$). In contrast to startle amplitude, there was no overall effect of substrain on percent PPI (Fig. 5B).

In summary, DBA/2Hsd mice display decreased inhibition of auditory evoked potentials despite a lack of difference in the overall amplitude of auditory evoked response or
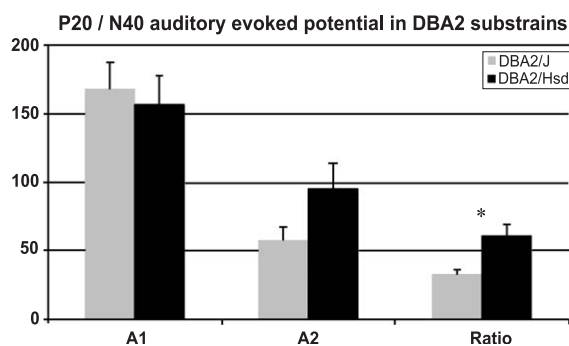

Fig. 4. Mean amplitude ($\pm$ S.E.M.) of response to the first stimulus (A1), second stimulus (A2) and ratio of A2/A1 for DBA/2J (gray) and DBA/2Hsd (black) mice. Note that there is no statistical difference between substrains on the amplitude of A1 or A2. However, DBA/2Hsd mice display an increased ratio of response (A2/A1), indicating less gating of the second response. Means $\pm$ S.D. for A1, A2 and the ratio of A2/A1 are displayed for DBA/2Hsd and DBA/2J mice.
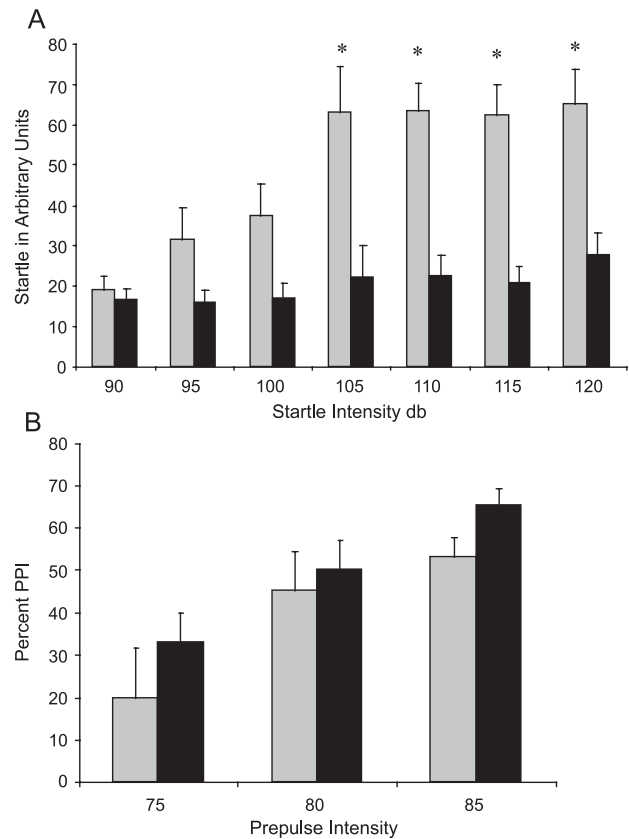

Fig. 5. (A) Acoustic Startle in DBA/2Hsd mice and DBA/2J. Startle scores (mean $\pm$ S.E.M.) are produced by a 40-ms startle stimulus alone in DBA/2Hsd (black) and DBA/2J (gray) mice. Asterisk indicates significant differences between the substrains. (B) Prepulse inhibition of startle in DBA/2Hsd and DBA/2J mice. DBA/2Hsd (black) and DBA/2J (gray). In contrast to acoustic startle, there are no differences in PPI between the two substrains of mice.

amplitude of response to the initial stimulus, suggesting a specific deficit in sensory inhibitory mechanisms rather than auditory sensitivity or neuronal excitability. Alternatively, DBA/2Hsd mice exhibited decreased startle relative to DBA/2J mice without a difference in prepulse inhibition of this motor response, suggesting that the motor gating effects of a weak prepulse do not differ between the substrains.

5. Discussion

Multiple studies have proposed that DBA/2 mice are an appropriate model for the neurobiological abnormalities in schizophrenia [14,43,54,55,69,70,71,72,73,76] These studies have relied upon the observation that DBA/2 mice share several endophenotypes that are seen in people with schizophrenia, including reduced PPI, reduced gating of the P20/N40 evoked potential and decreased P3a following a deviant tone. These animal models of schizophrenia have been interpreted to indicate that DBA/2 mice may possess some relevant genetic characteristics that are informative about a

potential genetic predisposition for schizophrenia in people. An example of this approach has equated low expression of the α-7 NAChR subunit in DBA/2 mice with similar reduced expression in schizophrenia. Data in the current study suggest that findings in DBA/2Hsd mice do not extend to the DBA/2J substrain. As such, any relevant genetic or neurobiological determinants of schizophrenia-like patterns of behavior in DBA/2Hsd mice may also differ in DBA/2J mice. Therefore, the subtle differences among these two closely related substrains are important in that they are more likely to distinguish relevant from incidental correlations between neurobiological and genetic factors and endophenotypes that are seen in schizophrenia.

5.1. Interpretation of evoked potentials

Not all studies using DBA/2 mice have found deficits in auditory processing. For example, Ehlers and colleagues recently showed that DBA/2 mice have enhanced P3a relative to C57BL/6 mice in response to a deviant tone, while we found DBA/2J mice to have decreased P3 activity as compared to C3H/HeJ mice without a significant difference from C57BL/6J [16,69]. One key difference between these studies arose from the definition of latency for the mouse P3, highlighting the importance of clarifying the temporal relationship between analogous components of the mouse and human evoked potentials.

The human P50 is a positive deflection occurring at approximately 50 ms after an auditory stimulus and has been defined as the first component that displays decreased amplitude following repetitive stimuli [26]. A similar component is seen in mice at 20 ms after the stimulus and is termed the P20. Following the P50, there is a negative deflection at approximately 100 ms, termed the N100 in humans [52]. An analogous component is seen in mice, occurring at approximately 40 ms, and is therefore termed

the N40. The P2 in humans occurs at approximately 200 ms and is an obligatory component of the human auditory evoked potential [52]. Recent data from our group using a principal component analysis indicate that there is a mouse analogue of this human component that occurs at approximately 80 ms, and we have thus called the P80 [69]. Following the P2, there is a novelty-responsive peak at approximately 300 ms in humans termed the P3 [52,81–83]. While we believe that a similar component is present at approximately 120 ms, others have proposed that the mouse P3a occurs at approximately 250 ms [16,69]. The earlier component was identified by our group using C57BL/6, C3H and DBA/2 mice and was responsive to change in stimulus tone, while the later component identified by Ehlers and colleagues in DBA/2 and C57BL6 responded to changes in stimulus probability but tone or amplitude. Interestingly, DBA/2 mice had decreased amplitude of the novelty related P120 relative to C3H/HeJ, suggesting that they display several electrophysiological phenotypes of schizophrenia [69].

The evoked potential response to auditory stimuli has been extensively studied in humans with abnormalities being found among schizophrenia patients in several components, including P50, N100, P2, and novelty related P3 described above [6,23,52,65,67,81–83]. The current study examines the P20/N40 between two substrains of DBA/2 mice, which have been proposed a model for gating abnormalities in humans [73]. Previous studies have referred to the mouse P20/N40 as a complex that is gated in a fashion similar to the human P50 [73]. However, we believe that these components are analogues to the P50 and N100, respectively. Fig. 6 demonstrates these similarities in the human and mouse auditory evoked potentials, with the latencies of each mouse component being approximately 40% of their human counterpart. Additionally, a recent study in our laboratory indicates that the mouse N40
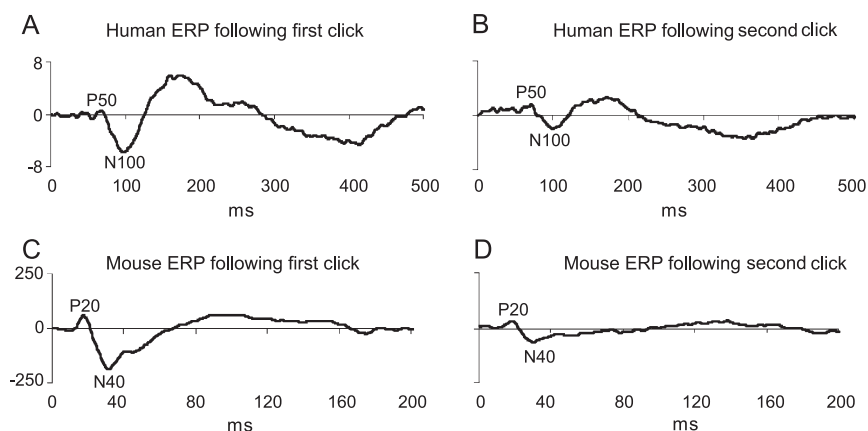

Fig. 6. Example of human and mouse auditory evoked potentials from a paired stimulus gating paradigm. As is evident, the morphology and response characteristics of the mouse AEP matches well with that of the human for both the first and second stimulus. The mouse AEP consist of a peak at 20 ms termed the P20, followed by a trough at 40 ms, termed the N40. These evoked responses in mice correspond to the human P50 and N100 with the latencies of the mouse response being approximately 40% of their human counterpart. EEG data was filtered with a 1,500 Hz band pass filter. Note that the amplitude of responses is smaller in human reflecting the use of scalp EEG rather than depth electrodes in mice.

displays a response relationship between amplitude and interstimulus interval between 0.25 and 8 s similar to the human N100. This analysis also indicates that the mouse P20 and P80 do not display significant changes in amplitude over this range of interstimulus intervals in accordance with the human P50 and P200, respectively [51]. Whether the mouse P20/N40 is similar to the human P50 as previously posited, or the P50 and N100 as we believe, it serves as a model for inhibitory processes in the auditory pathway. This process is impaired in people with schizophrenia for both the P50 and N100 components. Further study to map the cerebral generators of these individual components would elucidate the specific relationship between auditory evoked components in mice and humans and improve the ability to link the biology and genetic determinants of this phenotype.

As evident in Fig. 2, the amplitudes of both the P20 and N40 are reduced, or gated, in response to the second stimulus in the paired stimulus paradigm. This characteristic response to repeated, equivalent stimuli is thought to invoke local circuit inhibition in the hippocampus that reduces the response to the second stimulus [25,31]. This local circuit inhibition is thought to be elicited by septal input to hippocampal pyramidal cells and GABAergic interneurons that contain α7-Nicotinic Acetylcholine receptors. The expression of these receptors has been shown to vary between people with schizophrenia and non-affected individuals as well as between inbred strains of mice [26,73]. Thus, while both of these substrains are classified as DBA/2 by microsatellite DNA markers, it is possible that they differ for the expression or localization of hippocampal α7-Nicotinic receptors. Future studies will attempt to isolate the mechanisms responsible for differences in sensory processing demonstrated in the current study.

Sensory gating of auditory evoked potentials and prepulse inhibition of startle have both been used to study specific deficits in processing and modulation of sensory stimuli. Although both models are used as measures of gating of a response following an auditory stimulus, it is important to note that they do not assess equivalent circuits and neuronal processes. As the current data indicate, two substrains of DBA/2 mice differ in the gating of evoked potentials, with the DBA/2J substrain demonstrating enhanced gating relative to DBA/2Hsd mice. However, no differences were found on the sensorimotor gating task of PPI of startle. This is consistent with several studies in humans and rats that have also reported that these tasks are not equivalent [15,17,66]. As such, it is possible that PPI is related to gating of motor responses while inhibition of evoked potentials is related to inhibitory processes purely within sensory systems.

Although these results suggest that there may be genetic differences in DBA/2J and DBA/2Hsd inbred mouse substrains, one limitation to our design results from different rearing environments at Jackson and Harlan Laboratories. To explore this possibility, we plan to breed DBA/2J and DBA/2Hsd substrains at the University of Pennsylvania to investigate whether or not the observed phenotypic differences are perseveered under identical rearing location. Inhibition of evoked potentials and PPI of startle will then be examined in offspring from both strains raised in identical environments to further characterize proposed genetic differences. An additional consideration is that epigenetic factors such as maternal rearing style have been shown to influence behaviors and physiology in adult offspring [86]. Therefore, subsequent experiments could employ cross-fostering strategies to investigate the role of maternal rearing on later expression of sensory and sensorimotor behaviors. It is also possible that differences between the substrains for inhibition of evoked potentials result from differential sensitivity to toxic effects of ketamine. However, all testing of evoked potentials was done 7 days after a single exposure to ketamine and previous reports indicate that ketamine does not alter gating of evoked potentials [15]. Conversely, that same study concluded that acute administration of ketamine altered PPI of startle, again highlighting the differences between these two measures. Of note, animals used for startle and PPI in the current study were not exposed to ketamine at any time. Additionally, studies in humans suggest that the amplitude of auditory evoked potential and PPI of startle are correlated when examined within the same individuals [66]. Our results demonstrating no difference between substrains for either the amplitude of evoked potentials or PPI of startle are consistent with this observation and support the idea that gating of evoked potentials and gating of motor responses are distinct neuronal processes.

Because a number of previous studies describe high-frequency ($\sim$ 12,000–20,000 Hz) hearing loss in many inbred mouse strains including DBA/2, we have incorporated this concern in our experimental design [12,18,19,41,84,88–90,92–94]. Specifically, the current study utilized a 1500 Hz stimulus rather than the high frequency stimuli that are maximally affected in the type of hearing loss that occurs in mice. While mice do not demonstrate maximal sensitivity to such low frequency tones, the 1500 Hz stimuli used are not experienced subjectively as pure tones due to the 10 ms duration. A previous study successfully recorded ERPs in DBA/2 and C57BL/6 mice over a range of frequencies from 1 to 15 kHz at intensities lower than those used in this study [16]. Earlier studies by our group to examine novel pitch detection utilized stimuli of 50 ms duration specifically to allow for the detection of tonal differences [69]. Additionally, the presence of an N1 evoked potential signifies that the stimulus has reached auditory cortex [33]. Although the presence of such evoked potentials demonstrate, by definition, that both substrains can hear the ERP stimuli, we cannot rule out that one substrain may be able to hear stimuli below the 58 dB we were able to measure. However, given the lack of difference in amplitude of evoked potentials to the first stimulus, it is unlikely that differences in

sensitivity below 58 dB account for the difference in gating of the ERP at 80 dB. Additionally, the lack of a difference in PPI also suggests that the effect of non-startling prepulses did not differ between substrains, whereas a difference in auditory threshold would be most apparent at the lowest intensities. The age of testing was also chosen to avoid the effects of age-related hearing loss. A comprehensive review of strains at Jackson labs determined that DBA/2J mice have an ABR threshold of 55 dB at 8 weeks of age, which is consistent with several other studies in DBA/2 mice [88,91,95,97]. Similarly, ABR measurements in DBA/2J and DBA/2Hsd in the current study indicate that both substrains are able to hear stimuli at 58 dB, which is more than 20 dB below the intensity used in ERP testing. These data indicate that the difference in gating of evoked potentials observed between these sub-strains stem from alterations in the processing of the auditory stimuli that are likely relevant to gating deficits found in schizophrenia, rather than to any differences in auditory sensitivity.

In summary, the current study demonstrates that DBA/2J and DBA/2Hsd mice differ on two key phenotypes that have been used as animal models for schizophrenia. These data suggest that differences between these strains may allow for a more selective dissection of the genetic, neurobiological and perhaps environmental factors that contribute to the expression and transmission of schizophrenia. As such, future studies comparing these closely related substrains are indicated.

Acknowledgements

References

[1] G. Adler, W.F. Gattaz, Auditory evoked potentials in schizophrenic patients before and during neuroleptic treatment. Relationship to psychopathological state, Eur. Arch. Psychiatry Clin. Neurosci. 242 (1993) 357–361.

[2] G. Adler, J. Adler, M. Schneck, B. Armbruster, Influence of stimulation parameters on auditory stimulus processing in schizophrenia and major depression: an auditory evoked potential study, Acta Psychiatr. Scand. 81 (1990) 453–458.

[3] L.E. Adler, L.J. Hoffer, J. Griffith, M.C. Waldo, R. Freedman, Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics, Biol. Psychiatry 32 (1992) 607–616.

[4] V.P. Bakshi, M. Tricklebank, H.C. Neijt, V. Lehmann-Masten, M.A. Geyer, Disruption of prepulse inhibition and increases in locomotor activity by competitive N-methyl-D-aspartate receptor antagonists in rats, J. Pharmacol. Exp. Ther. 288 (1999) 643–652.

[5] N. Boutros, H. Nasrallah, R. Leighty, M. Torello, P. Tueting, S. Olson, Auditory evoked potentials, clinical vs. research applications, Psychiatry Res. 69 (1997) 183–195.

[6] N.N. Boutros, A. Belger, D. Campbell, C. D'Souza, J. Krystal, Comparison of four components of sensory gating in schizophrenia and normal subjects: a preliminary report, Psychiatry Res. 88 (1999) 119–130.

[7] D.L. Braff, M.A. Geyer, Sensorimotor gating and schizophrenia. Human and animal model studies, Arch. Gen. Psychiatry 47 (1990) 181–188.

[8] A.E. Bullock, B.S. Slobe, V. Vazquez, A.C. Collins, Inbred mouse strains differ in the regulation of startle and prepulse inhibition of the startle response, Behav. Neurosci. 111 (1997) 1353–1360.

[9] K.S. Cadenhead, G.A. Light, M.A. Geyer, D.L. Braff, Sensory gating deficits assessed by the P50 event-related potential in subjects with schizotypal personality disorder, Am. J. Psychiatry 157 (2000) 55–59.

[10] N.M. Canal, R. Gourevitch, G. Sandner, Non-monotonic dependency of PPI on temporal parameters: differential alteration by ketamine and MK-801 as opposed to apomorphine and DOI, Psychopharmacology (Berl.) 156 (2001) 169–176.

[11] S.V. Catts, A.M. Shelley, P.B. Ward, B. Liebert, N. McConaghy, S. Michie, P.T. Michie, Brain potential evidence for an auditory sensory memory deficit in schizophrenia, Am. J. Psychiatry 152 (1995) 213–219.

[12] M.W. Church, D.W. Shucard, Age-related hearing loss in BDF1 mice as evidenced by the brainstem auditory evoked potential, Audiology 25 (1986) 363–372.

[13] J.D. Cook, E.H. Ellinwood Jr., W.P. Wilson, Auditory habituation at primary cortex as a function of stimulus rate, Exp. Neurol. 21 (1968) 167–175.

[14] J.N. Crawley, J.K. Belknap, A. Collins, J.C. Crabbe, W. Frankel, N. Henderson, R.J. Hitzemann, S.C. Maxson, L.L. Miner, A.J. Silva, J.M. Wehner, A. Wynshaw-Boris, R. Paylor, Behavioral phenotypes of inbred mouse strains: implications and recommendations for molecular studies, Psychopharmacology (Berl.) 132 (1997) 107–124.

[15] N.M. de Bruin, B.A. Ellenbroek, A.R. Cools, A.M. Coenen, E.L. van Luijtelaar, Differential effects of ketamine on gating of auditory evoked potentials and prepulse inhibition in rats, Psychopharmacology (Berl.) 142 (1999) 9–17.

[16] C.L. Ehlers, C. Somes, Long latency event-related potentials in mice: effects of stimulus characteristics and strain, Brain Res. 957 (2002) 117–128.

[17] B.A. Ellenbroek, G. van Luijtelaar, M. Frenken, A.R. Cools, Sensory gating in rats: lack of correlation between auditory evoked potential gating and prepulse inhibition, Schizophr. Bull. 25 (1999) 777–788.

[18] L.C. Erway, J.F. Willott, J.R. Archer, D.E. Harrison, Genetics of age-related hearing loss in mice: I. Inbred and F1 hybrid strains, Hear. Res. 65 (1993) 125–132.

[19] L.C. Erway, Y.W. Shiau, R.R. Davis, E.F. Krieg, Genetics of age-related hearing loss in mice: III. Susceptibility of inbred and F1 hybrid strains to noise-induced hearing loss, Hear. Res. 93 (1996) 181–187.

[20] R.J. Erwin, M. Mawhinney-Hee, R.C. Gur, R.E. Gur, Midlatency auditory evoked responses in schizophrenia, Biol. Psychiatry 30 (1991) 430–442.

[21] R.J. Erwin, B.I. Turetsky, P. Moberg, R.C. Gur, R.E. Gur, P50 abnormalities in schizophrenia: relationship to clinical and neuropsychological indices of attention, Schizophr. Res. 33 (1998) 157–167.

[22] D. Feifel, K. Priebe, The effects of subchronic haloperidol on intact and dizocilpine-disrupted sensorimotor gating, Psychopharmacology (Berl.) 146 (1999) 175–179.

[23] R. Freedman, L.E. Adler, M.C. Waldo, E. Pachtman, R.D. Franks, Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: comparison of medicated and drug-free patients, Biol. Psychiatry 18 (1983) 537–551.

[24] R. Freedman, L.E. Adler, P. Bickford, W. Byerley, H. Coon, C.M. Cullum, J.M. Griffith, J.G. Harris, S. Leonard, C. Miller, et al., Schizophrenia and nicotinic receptors, Harv. Rev. Psychiatry 2 (1994) 179–192 (Review, 90 refs).

[25] R. Freedman, L.E. Adler, M. Myles-Worsley, H.T. Nagamoto, C. Miller, M. Kisley, K. McRae, E. Cawthra, M. Waldo, Inhibitory gating of an evoked response to repeated auditory stimuli in schizophrenic and normal subjects. Human recordings, computer simu-

lation, and an animal model, Arch. Gen. Psychiatry 53 (1996) 1114–1121.

[26] R. Freedman, C.E. Adams, S. Leonard, The alpha7-nicotinic acetylcholine receptor and the pathology of hippocampal interneurons in schizophrenia, J. Chem. Neuroanat. 20 (2000) 299–306.

[27] T. Frodl, E.M. Meisenzahl, J. Gallinat, U. Hegerl, H.J. Moller, Markers from event-related potential subcomponents and reaction time for information processing dysfunction in schizophrenia, Eur. Arch. Psychiatry Clin. Neurosci. 248 (1998) 307–313.

[28] Y. Furuya, H. Ogura, Competitive NMDA and strychnine-insensitive glycine-site antagonists disrupt prepulse inhibition, Pharmacol. Biochem. Behav. 57 (1997) 909–913.

[29] M.A. Geyer, D.L. Braff, Startle habituation and sensorimotor gating in schizophrenia and related animal models, Schizophr. Bull. 13 (1987) 643–668.

[30] U. Hegerl, W. Gaebel, H. Gutzman, G. Ulrich, Auditory evoked potentials as possible predictors of outcome in schizophrenic outpatients, Int. J. Psychophysiol. 6 (1988) 207–214.

[31] K.M. Hershman, R. Freedman, P.C. Bickford, GABAB antagonists diminish the inhibitory gating of auditory response in the rat hippocampus, Neurosci. Lett. 190 (1995) 133–136.

[32] C.Y. Hsieh, S.J. Cruikshank, R. Metherate, Differential modulation of auditory thalamocortical and intracortical synaptic transmission by cholinergic agonist, Brain Res. 880 (2000) 51–64.

[33] M. Hyde, The N1 response and its applications, Audiol. Neuro-otol. 2 (1997) 281–307.

[34] D.C. Javitt, P. Doneshka, I. Zylberman, W. Ritter , H.G. Vaughan Jr., Impairment of early cortical processing in schizophrenia: an event-related potential confirmation study, Biol. Psychiatry 33 (1993) 513–519.

[35] D.C. Javitt, M. Steinschneider, C.E. Schroeder, J.C. Arezzo, Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 11962–11967.

[36] D.C. Javitt, M. Jayachandra, R.W. Lindsley, C.M. Specht, C.E. Schroeder, Schizophrenia-like deficits in auditory P1 and N1 refractoriness induced by the psychomimetic agent phencyclidine (PCP), Clin. Neurophysiol. 111 (2000) 833–836.

[37] M.L. Jongsma, C.M. van Rijn, W.J. van Schaijk, A.M. Coenen, Effects of diazepam on auditory evoked potentials of rats elicited in a ten-tone paradigm, Neuropsychobiology 42 (2000) 158–162.

[38] C. King, T. McGee, E.W. Rubel, T. Nicol, N. Kraus, Acoustic features and acoustic changes are represented by different central pathways, Hear. Res. 85 (1995) 45–52.

[39] G.G. Kinney, L.O. Wilkinson, K.L. Saywell, M.D. Tricklebank, Rat strain differences in the ability to disrupt sensorimotor gating are limited to the dopaminergic system, specific to prepulse inhibition, and unrelated to changes in startle amplitude or nucleus accumbens dopamine receptor sensitivity, J. Neurosci. 19 (1999) 5644–5653.

[40] M.H. Kodsi, N.R. Swerdlow, Quinolinic acid lesions of the ventral striatum reduce sensorimotor gating of acoustic startle in rats, Brain Res. 643 (1994) 59–65.

[41] J. Kulig, J.F. Willott, Frequency difference limens of C57BL/6 and DBA/2 mice: relationship to auditory neuronal response properties and hearing impairment, Hear. Res. 16 (1984) 169–174.

[42] E. LaBossiere, M. Glickstein, Histological Processing for the Neural Science, Charles C. Thomas, Springfield, 1976, pp. 41–43.

[43] S. Leonard, C. Adams, C.R. Breese, L.E. Adler, P. Bickford, W. Byerley, H. Coon, J.M. Griffith, C. Miller, M. Myles-Worsley, H.T. Nagamoto, Y. Rollins, K.E. Stevens, M. Waldo, R. Freedman, Nicotinic receptor function in schizophrenia, Schizophr. Bull. 22 (1996) 431–445.

[44] V.V. Loginov, I.P. Leshchinskaia, L.P. Latash, EEG of the interstimulus intervals during habituation of auditory evoked potentials in depressive moods, Zh. Vyssh. Nerv. Deiat. Im I P Pavlova 37 (1987) 866–874.

[45] R.S. Mansbach, Effects of NMDA receptor ligands on sensorimotor gating in the rat, Eur. J. Pharmacol. 202 (1991) 61–66.

[46] B.A. Martin, D. Kurtzberg, D.R. Stapells, The effects of decreased audibility produced by high-pass noise masking on N1 and the mismatch negativity to speech sounds /ba/and/da, J. Speech Lang. Hear. Res. 42 (1999) 271–286.

[47] Z.A. Martinez, N.D. Halim, J.L. Oostwegel, M.A. Geyer, N.R. Swerdlow, Ontogeny of phencyclidine and apomorphine-induced startle gating deficits in rats, Pharmacol. Biochem. Behav. 65 (2000) 449–457.

[48] Z.A. Martinez, J. Oostwegel, M.A. Geyer, G.D. Ellison, N.R. Swerdlow, "Early" and "late" effects of sustained haloperidol on apomorphine- and phencyclidine-induced sensorimotor gating deficits, Neuropsychopharmacology 23 (2000) 517–527.

[49] Z.A. Martinez, A. Platten, E. Pollack, J. Shoemaker, H. Ro, L. Pitcher, M.A. Geyer, N.R. Swerdlow, "Typical" but not "atypical" antipsychotic effects on startle gating deficits in prepubertal rats, Psychopharmacology (Berl.) 161 (2002) 38–46.

[50] D.H. Mathalon, J.M. Ford, A. Pfefferbaum, Trait and state aspects of P300 amplitude reduction in schizophrenia: a retrospective longitudinal study, Biol. Psychiatry 47 (2000) 434–449.

[51] C. Maxwell, Y. Liang, B. Weightman, S. Kanes, E. Abel, R. Gur, B. Turetsky, W. Bilker, R. Lenox, S. Siegel, Effects of chronic olanzapine and haloperidol differ on the mouse N1 auditory evoked potential (in review).

[52] R.W. McCarley, S.F. Faux, M.E. Shenton, P.G. Nestor, J. Adams, Event-related potentials in schizophrenia: their biological and clinical correlates and a new model of schizophrenic pathophysiology, Schizophr. Res. 4 (1991) 209–231.

[53] C.R. Mitchell, J.B. Kempton, T.A. Creedon, D.R. Trune, The use of a 56-stimulus train for the rapid acquisition of auditory brainstem responses, Audiol. Neuro-otol. 4 (1999) 80–87.

[54] B. Olivier, C. Leahy, T. Mullen, R. Paylor, V.E. Groppi, Z. Sarnyai, D. Brunner, The DBA/2J strain and prepulse inhibition of startle: a model system to test antipsychotics? Psychopharmacology (Berl.) 156 (2001) 284–290.

[55] R. Paylor, J.N. Crawley, Inbred strain differences in prepulse inhibition of the mouse startle response, Psychopharmacology (Berl.) 132 (1997) 169–180.

[56] T.W. Picton, S.A. Hillyard, Human auditory evoked potentials: II. Effects of attention, Electroencephalogr. Clin. Neurophysiol. 36 (1974) 191–199.

[57] T.W. Picton, S.A. Hillyard, H.I. Krausz, R. Galambos, Human auditory evoked potentials: I. Evaluation of components, Electroencephalogr. Clin. Neurophysiol. 36 (1974) 179–190.

[58] Z. Pincze, P. Lakatos, C. Rajkai, I. Ulbert, G. Karmos, Separation of mismatch negativity and the N1 wave in the auditory cortex of the cat: a topographic study, Clin. Neurophysiol. 112 (2001) 778–784.

[59] R.J. Ralph, G.B. Varty, M.A. Kelly, Y.M. Wang, M.G. Caron, M. Rubinstein, D.K. Grandy, M.J. Low, M.A. Geyer, The dopamine D2, but not D3 or D4, receptor subtype is essential for the disruption of prepulse inhibition produced by amphetamine in mice, J. Neurosci. 19 (1999) 4627–4633.

[60] M. Reite, P. Teale, J. Zimmerman, K. Davis, J. Whalen, Source location of a 50 msec latency auditory evoked field component, Electroencephalogr. Clin. Neurophysiol. 70 (1988) 490–498.

[61] W.T. Roth, A. Pfefferbaum, T.B. Horvath, P.A. Berger, B.S. Kopell, P3 reduction in auditory evoked potentials of schizophrenics, Electroencephalogr. Clin. Neurophysiol. 49 (1980) 497–505.

[62] T. Ruusuvirta, From spatial acoustic changes to attentive behavioral responses within 200 ms in humans, Neurosci. Lett. 275 (1999) 49–52.

[63] T. Ruusuvirta, T. Korhonen, M. Penttonen, J. Arikoski, K. Kivirikko, Behavioral and hippocampal evoked responses in an auditory oddball situation when an unconditioned stimulus is paired with deviant tones in the cat: experiment II, Int. J. Psychophysiol. 20 (1995) 41–47.

[64] T. Ruusuvirta, T. Korhonen, M. Penttonen, J. Arikoski, K. Kivirikko, Hippocampal event-related potentials to pitch deviances in an audi-

tory oddball situation in the cat: experiment I, Int. J. Psychophysiol. 20 (1995) 33–39.

[65] U. Schall, S.V. Catts, F. Karayanidis, P.B. Ward, Auditory event-related potential indices of fronto-temporal information processing in schizophrenia syndromes: valid outcome prediction of clozapine therapy in a three-year follow-up, Int. J. Neuropsychopharmcol. 2 (1999) 83–93.

[66] S.B. Schwarzkopf, J.S. Lamberti, D.A. Smith, Concurrent assessment of acoustic startle and auditory P50 evoked potential measures of sensory inhibition, Biol. Psychiatry 33 (1993) 815–828.

[67] C. Siegel, M. Waldo, G. Mizner, L.E. Adler, R. Freedman, Deficits in sensory gating in schizophrenic patients and their relatives. Evidence obtained with auditory evoked responses, Arch. Gen. Psychiatry 41 (1984) 607–612.

[68] S.J. Siegel, R.H. Lenox, R.E. Gur, B.I. Turetsky, Sensory gating and mismatch negativity in schizophrenia and mice, Proc. Soc. Neurosci. (2001) 663.

[69] S.J. Siegel, P. Connolly, Y. Liang, R.H. Lenox, R.E. Gur, W.B. Bilker, S.J. Kanes, B.I. Turetsky, Effects of strain, novelty, and NMDA blockade on auditory-evoked potentials in mice, Neuropsychopharmacology 28 (2003) 675–682.

[70] J.K. Simosky, K.E. Stevens, W.R. Kem, R. Freedman, Intragastric DMXB-A, an alpha7 nicotinic agonist, improves deficient sensory inhibition in DBA/2 mice, Biol. Psychiatry 50 (2001) 493–500.

[71] J.K. Simosky, K.E. Stevens, L.E. Adler, R. Freedman, Clozapine improves deficient inhibitory auditory processing in DBA/2 mice, via a nicotinic cholinergic mechanism, Psychopharmacology (Berl.) 165 (2003) 386–396.

[72] K.E. Stevens, K.D. Wear, Normalizing effects of nicotine and a novel nicotinic agonist on hippocampal auditory gating in two animal models, Pharmacol. Biochem. Behav. 57 (1997) 869–874.

[73] K.E. Stevens, R. Freedman, A.C. Collins, M. Hall, S. Leonard, M.J. Marks, G.M. Rose, Genetic correlation of inhibitory gating of hippocampal auditory evoked response and α-bungerotoxin-binding nicotinic cholinergic receptors in inbred mouse strains, Neuropsychopharmacology 15 (1996) 152–162.

[74] K.E. Stevens, J. Luthman, E. Lindqvist, R.G. Johnson, G.M. Rose, Effects of neonatal dopamine depletion on sensory inhibition in the rat, Pharmacol. Biochem. Behav. 53 (1996) 817–823.

[75] K.E. Stevens, R.G. Johnson, G.M. Rose, Rats reared in social isolation show schizophrenia-like changes in auditory gating, Pharmacol. Biochem. Behav. 58 (1997) 1031–1036.

[76] K.E. Stevens, W.R. Kem, V.M. Mahnir, R. Freedman, Selective alpha7-nicotinic agonists normalize inhibition of auditory response in DBA mice, Psychopharmacology (Berl.) 136 (1998) 320–327.

[77] N.R. Swerdlow, M.A. Geyer, Using an animal model of deficient sensorimotor gating to study the pathophysiology and new treatments of schizophrenia, Schizophr. Bull. 24 (1998) 285–301.

[78] N.R. Swerdlow, D.L. Braff, N. Taaid, M.A. Geyer, Assessing the validity of an animal model of deficient sensorimotor gating in schizophrenic patients, Arch. Gen. Psychiatry 51 (1994) 139–154.

[79] L.M. Tarantino, T.J. Gould, J.P. Druhan, M. Bucan, Behavior and mutagenesis screens: the importance of baseline analysis of inbred strains, Mamm. Genome 11 (2000) 555–564.

[80] D.R. Trune, R.J. Wobig, J.B. Kempton, S.H. Hefeneider, Steroid treatment improves cochlear function in the MRL. MpJ-Fas(lpr) autoimmune mouse, Hear. Res. 137 (1999) 160–166.

[81] B. Turetsky, E.A. Colbath, R.E. Gur, P300 subcomponent abnormalities in schizophrenia: II. Longitudinal stability and relationship to symptom change, Biol. Psychiatry 43 (1998) 31–39.

[82] B.I. Turetsky, E.A. Colbath, R.E. Gur, P300 subcomponent abnormalities in schizophrenia: I. Physiological evidence for gender and subtype specific differences in regional pathology, Biol. Psychiatry 43 (1998) 84–96.

[83] B.I. Turetsky, T.D. Cannon, R.E. Gur, P300 subcomponent abnormalities in schizophrenia: III. Deficits In unaffected siblings of schizophrenic probands, Biol. Psychiatry 47 (2000) 380–390.

[84] J.G. Turner, J.F. Willott, Exposure to an augmented acoustic environment alters auditory function in hearing-impaired DBA/2J mice, Hear. Res. 118 (1998) 101–113.

[85] M. Velasco, F. Velasco, A.L. Velasco, Intracranial studies on potential generators of some vertex auditory evoked potentials in man, Stereotact. Funct. Neurosurg. 53 (1989) 49–73.

[86] I.C. Weaver, M. Szyf, M.J. Meaney, From maternal care to gene expression: DNA methylation and the maternal programming of stress responses, Endocr. Res. 28 (2002) 699.

[87] T.M. Welch, M.W. Church, D.W. Shucard, A method for chronically recording brain-stem and cortical auditory evoked potentials from unanesthetized mice, Electroencephalogr. Clin. Neurophysiol. 60 (1985) 78–83.

[88] J.F. Willott, L.C. Erway, Genetics of age-related hearing loss in mice: IV. Cochlear pathology and hearing loss in 25 BXD recombinant inbred mouse strains, Hear. Res. 119 (1998) 27–36.

[89] J.F. Willott, J.G. Turner, Prolonged exposure to an augmented acoustic environment ameliorates age-related auditory changes in C57BL/6J and DBA/2J mice, Hear. Res. 135 (1999) 78–88.

[90] J.F. Willott, K.R. Henry, F. George, Noise-induced hearing loss, auditory evoked potentials, and protection from audiogenic seizures in mice, Exp. Neurol. 46 (1975) 542–553.

[91] J.F. Willott, J. Kulig, T. Satterfield, The acoustic startle response in DBA/2 and C57BL/6 mice: relationship to auditory neuronal response properties and hearing impairment, Hear. Res. 16 (1984) 161–167.

[92] J.F. Willott, R.M. Demuth, S.M. Lu, Excitability of auditory neurons in the dorsal and ventral cochlear nuclei of DBA/2 and C57BL/6 mice, Exp. Neurol. 83 (1984) 495–506.

[93] J.F. Willott, S. Carlson, H. Chen, Prepulse inhibition of the startle response in mice: relationship to hearing loss and auditory system plasticity, Behav. Neurosci. 108 (1994) 703–713.

[94] J.F. Willott, L.C. Erway, J.R. Archer, D.E. Harrison, Genetics of age-related hearing loss in mice: II. Strain differences and effects of caloric restriction on cochlear pathology and evoked response thresholds, Hear. Res. 88 (1995) 143–155.

[95] J.F. Willott, J.G. Turner, S. Carlson, D. Ding, L. Seegers Bross, W.A. Falls, The BALB/c mouse as an animal model for progressive sensorineural hearing loss, Hear. Res. 115 (1998) 162–174.

[96] G.K. Wood, H. Tomasiewicz, U. Rutishauser, T. Magnuson, R. Quirion, J. Rochford, L.K. Srivastava, NCAM-180 knockout mice display increased lateral ventricle size and reduced prepulse inhibition of startle, NeuroReport 9 (1998) 461–466.

[97] Q.Y. Zheng, K.R. Johnson, L.C. Erway, Assessment of hearing in 80 inbred strains of mice by ABR threshold analyses, Hear. Res. 130 (1999) 94–107.