Deviance-elicited Changes in Event-related Potentials are Attenuated by Ketamine in Mice

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Abstract

■ **Background:** People with schizophrenia exhibit reduced ability to detect change in the auditory environment, which has been linked to abnormalities in *N*-methyl-D-aspartate (NMDA) receptor-mediated glutamate neurotransmission. This ability to detect changes in stimulus qualities can be measured with electroencephalography using auditory event-related potentials (ERPs). For example, reductions in the N100 and mismatch negativity (MMN), in response to pitch deviance, have been proposed as endophenotypes of schizophrenia. This study examines a novel rodent model of impaired pitch deviance detection in mice using the NMDA receptor antagonist ketamine. **Methods:** ERPs were recorded from unanesthetized mice during a pitch deviance paradigm prior to and following ketamine administration. First, N40 amplitude was evaluated using stimuli between 4 and 10 kHz to assess the amplitude of responses across the frequency range used. The amplitude and latency of the N40 were analyzed following standard (7 kHz) and deviant (5–9 kHz) stimuli. Additionally, we examined which portions of the ERP are selectively altered by pitch deviance to define possible regions for the mouse MMN. **Results:** Mice displayed increased N40 amplitude that was followed by a later negative component between 50 and 75 msec in response to deviant stimuli. Both the increased N40 and the late N40 negativity were attenuated by ketamine. Ketamine increased N40 latency for both standard and deviant stimuli alike. **Conclusions:** The mouse N40 and a subsequent temporal region have deviance response properties similar to the human N100 and, possibly, MMN. Deviance responses were abolished by ketamine, suggesting that ketamine-induced changes in mice mimic deviance detection deficits in schizophrenia. ■

INTRODUCTION

People with schizophrenia display reduced ability to detect changes in the auditory environment as measured with deviance-elicited event-related potentials (ERPs) including the N100 and mismatch negativity (MMN) (Light & Braff, 2005; Davalos, Kisley, Polk, & Ross, 2003; Michie, 2001; Javitt, Shelley, & Ritter, 2000; Umbricht et al., 2000; Shelley, Silipo, & Javitt, 1999; Javitt, Doneshka, Zylberman, Ritter, & Vaughan, 1993). This elementary ability to detect change in the environment can be reduced to a series of sequential operations, including (1) registration of a sensory input; (2) encoding of its qualitative features (such as pitch and duration); (3) formation of an echoic memory of the stimulus; (4) comparison of sequential inputs; followed by (5) the determination of deviance.

The P50 is a component of the human ERP that is thought to represent an automatic response that registers the presence of an auditory stimulus but does not vary substantially with attention or qualitative features of the stimulus (Ermutlu, Karamursel, Ugur, Senturk, & Gokhan, 2005; Jerger, Biggins, & Fein, 1992). The P50 is followed by the N100, a negative deflection which is sensitive to qualitative features such as pitch and intensity (Ahveninen et al., 2006; Restuccia, Della Marca, Marra, Rubino, & Valeriani, 2005; Shelley et al., 1999; Covington & Polich, 1996; Yingling & Nethercut, 1983). The MMN follows the N100 temporally and is manifest as an exaggerated negative deflection to a deviant stimulus relative to a repetitive one (Haenschel, Vernon, Dwivedi, Gruzelier, & Baldeweg, 2005; Javitt, Jayachandra, Lindsley, Specht, & Schroeder, 2000; May et al., 1999). The P300, a later ERP component, consisting of nontarget (P3a) and target (P3b) responses, reflects higher-order processing of deviance that surpasses a threshold to elicit orientation to salient change in the environment (Munka & Berti, 2006; Ceponiene et al., 2004; Winterer et al., 2003; Winterer, Egan, Radler, Coppola, & Weinberger, 2001; Cycowicz & Friedman, 1997). The majority of studies have found that people with schizophrenia show reductions in all of these ERP components (Winterer et al., 2001, 2003; Michie, 2001; Brown et al., 2000; Javitt, Jayachandra, et al., 2000; Laurent et al., 1999; Shelley et al., 1999; Oades, Dittmann-Balcar, Zerbin, & Grzella, 1997; Catts et al., 1995; Javitt et al., 1993; Shelley et al., 1991). Conversely, a few studies have found augmentation in ERPs recorded from people with the illness (Kathmann, von Recum, Haag, & Engel, 2000;

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Williams, Gordon, Wright, & Bahramali, 2000; Rockstroh, Muller, Wagner, Cohen, & Elbert, 1994).

Previous work has demonstrated that rodents share many similarities with humans for specific portions of the ERP, including mouse analogs of the P50, N100, P200, and P300 components. These components in mice are named the P20, N40, P80, and P120 for latency, and share both stimulus and pharmacologic response properties with the corresponding human potentials (Maxwell, Ehrlichman, Liang, Trief, et al., 2006; Umbricht, Vyssotki, Latanov, Nitsch, & Lipp, 2005; Maxwell, Liang, et al., 2004; Connolly et al., 2003; Siegel et al., 2003; Simosky, Stevens, Adler, & Freedman, 2003; Stevens, Kem, Mahnir, & Freedman, 1998). As such, mouse ERPs have been used in various pharmacological and genetic models for ERP endophenotypes of schizophrenia (e.g., deficits in gating) (Maxwell, Ehrlichman, Liang, Gettes, et al., 2006; Connolly et al., 2004; Maxwell, Kanes, Abel, & Siegel, 2004; Umbricht et al., 2004; Simosky, Stevens, Kem, & Freedman, 2001). Gating is a phenomenon where a reduction of ERP amplitude occurs to the second click of a paired-click paradigm compared to the first click when presented at a sufficiently short interstimulus interval. Although the majority of mouse studies have focused on amplitude and gating of ERPs, analysis of ERPs following the presentation of deviant stimuli may also prove useful in evaluating the neurobiology of abnormal sensory processing in schizophrenia. For example, the N100 and MMN ERP components display characteristic changes during deviance tasks in healthy controls but not in patients with schizophrenia (Brown et al., 2000; Boutros, Belger, Campbell, D'Souza, & Krystal, 1999). However, several investigators have noted difficulty separating the change in N100 and MMN following a deviant stimulus due to their close temporal and often overlapping nature (Sabri, Labelle, Gosselin, & Campbell, 2003; Pincze, Lakatos, Rajkai, Ulbert, & Karmos, 2001, 2002). Deviance-related ERPs can also be measured in mice to model deficits in the N100 and MMN to deviant tones in schizophrenia.

The MMN is elicited when the qualitative features of a deviant tone fail to match the pattern of a previous series of repetitive tones (Light & Braff, 2005; Javitt, Jayachandra, et al., 2000; Javitt, Shelley, et al., 2000). Therefore, deviance detection requires the ability to encode and store the previous auditory information to have a comparator against which change is measured. This initial phase of encoding is thought to occur in the primary auditory cortex and is manifest as the N100 in humans (Hyde, 1997). Accordingly, a failure to augment the N100 following a deviant stimulus could result from either a deficit in encoding the qualitative features of the standard stimulus or an inability to store those features for later comparison with the deviant. The lack of an MMN following a deviant stimulus may result from either failure to establish echoic memory for the standard stimuli or inability to detect a deviation from that standard. Models of MMN proposed by Javitt (2000), Javitt, Grochowski, Shelley, and Ritter (1998), Javitt, Steinschneider, Schroeder, and Arezzo (1996), Javitt, Doneshka, Grochowski, and Ritter (1995), and Javitt et al. (1993) have stressed the importance of *N*-methyl-D-aspartate (NMDA) receptors serving as comparators, rather than in initiating the memory trace. These models are based upon the idea that the resting NMDA receptor is blocked by magnesium, but ensembles of neurons can become unblocked or disinhibited through exposure of a prior stimulus. Thus, MMN represents current through unblocked, open NMDA receptors. In addition, Ruusuvirta, Huotilainen, and Näätänen (2007), Näätänen and Winkler (1999), Näätänen and Alho (1995, 1997), and Näätänen, Jiang, Lavikainen, Reinikainen, and Paavilainen (1993) have provided further support for the critical role of NMDA receptor disinhibition during the presentation of sequential standard stimuli for eliciting an MMN. It has been further proposed that GABAergic interneurons provide tonic inhibition of MMN-generating pyramidal cells at rest. These GABAergic interneurons then become inhibited during repeated standard stimuli producing disinhibition and generation of MMN. Therefore, two plausible targets for NMDA receptor modulation of MMN include a reduction in the response to the deviant tone or a loss of tonic inhibition, resulting in an increase in response to the standard tones.

Previous investigators have proposed that using multiple electrophysiological endophenotypes of schizophrenia will allow for improved diagnosis in humans (Price et al., 2005). Applying that logic to animal models, the current study builds upon previous work in humans, nonhuman primates, and smaller animals to advance a mouse model of deviance-related ERPs that offer the potential to broaden the methods with which to study pharmacological and genetic manipulations (Umbricht, Koller, Vollenweider, & Schmid, 2002; Javitt, Jayachandra, et al., 2000; Javitt, Shelley, et al., 2000; Ruusuvirta, 1999; Kraus, McGee, Carrell, et al., 1994; Kraus, McGee, Littman, Nicol, & King, 1994). Previous investigators have noted the need to develop rodent models of MMN deficits in schizophrenia (Lazar & Metherate, 2003). A recent study by Umbricht et al. (2005) demonstrated a duration-elicited MMN in mice, suggesting that this component may be a useful model of sensory processing abnormalities in schizophrenia. Umbricht et al. also noted several limitations in applying this model to frequency-elicited MMN in mice. Here, we address those limitations by proposing a model for frequency-dependent ERP alterations in mice using a task that presents a random set of deviant tones such that the mean frequencies of the standard and deviant tones are equal. Furthermore, we examine the effects of the NMDA receptor antagonist ketamine on deviance-related components.

METHODS

Animals

Twenty-seven DBA/2Hsd (DBA/2) mice were obtained from Harlan (Indianapolis, IN) at 8 weeks of age. All

testing was conducted between 10 and 13 weeks of age corresponding to a human age range for postpubescent, fully grown, young adults. All protocols were performed in accordance with University Laboratory Animal Resources guidelines and were approved by the Institutional Animal Care and Use Committee. Mice were housed three to four per cage in a light- and temperature-controlled Association for Assessment and Accreditation of Laboratory Animal Care–accredited animal facility. All efforts were made to minimize animal number and suffering. Water and standard rodent chow were available ad lib. Experiments were conducted at the University of Pennsylvania during the light phase between the hours of 0900 and 1300. Mice were acclimated to the housing facility for at least 1 week prior to all procedures.

Treatment Groups

The effects of NMDA receptor blockade were examined using ketamine. This portion of the study followed a within-group design in which each mouse was used in the following conditions: vehicle and 10 mg/kg ketamine ip (n = 8). This dose of ketamine was chosen based on previous dose–response studies (Maxwell, Ehrlichman, Liang, Trief, et al., 2006; Connolly et al., 2004; Siegel et al., 2003).

Surgery

Animals underwent stereotaxic implantation of electrode assemblies (PlasticsOne, Roanoke, VA) for non-anesthetized recording of auditory ERPs. The surgical procedure has been previously reported (Connolly et al., 2003, 2004; Maxwell, Liang, et al., 2004; Siegel et al., 2003). Briefly, animals were anesthetized with isoflurane and unipolar recording electrodes were placed in the CA3 hippocampal region (1.4 mm posterior, 2.65 mm lateral, and 2.75 mm deep relative to the bregma) and referenced to the ipsilateral frontal sinus. The electroencephalogram (EEG) recorded from this configuration will strongly reflect hippocampal activity. Other generators will influence the EEG as an inverse function of their distance from the recording site. ERPs recorded from this electrode configuration are characteristically similar in appearance to human recordings from the Cz scalp location as illustrated in the third figure from a prior publication by our group (Siegel et al., 2003). The electrode pedestal was secured to the skull using dental cement and super glue. EEGs were recorded 2 weeks after electrode surgery, as described below.

Recording

The recording session consisted of a drug-naive trial with an intraperitoneal injection of saline, which preceded an injection of ketamine for a total of two trials per mouse. Trials began 5 min after and concluded within 15 min of injection, consistent with one-half life of ketamine in this strain (Maxwell, Ehrlichman, Liang, Trief, et al., 2006). The trials were recorded during the light cycle, which corresponds to the normal resting period of the mice. Stimuli were generated by Micro1401 hardware and Spike 5 software (Cambridge Electronic Design, Cambridge, England) and were delivered through speakers attached to the cage top.

The stimulus protocol consisted of 24 standard tones (7 kHz) followed by a deviant tone that ranged from 5 to 9 kHz in 100-Hz increments. All tones were sinusoidal, 50 msec in duration, and separated by a 500-msec interstimulus interval. The order of deviant tones was randomly selected so that half were higher and half lower frequency than the standard tone. Consequently, the mean frequencies of the standard and deviant tones were equal. Each tone was used only once for a total of 40 sets of standard–deviant trials at 85 dB SPL. The sound pressure was calibrated inside the cage from the approximate height of the animal's head with a sound-level meter (Radio Shack, Cat. No. 33-2055) set to fast sample, max range, weighting A. Waveforms were filtered between 1 and 500 Hz, baseline corrected at stimulus onset, and individual sweeps were rejected for movement artifact based on a criteria of two times the root mean squared amplitude per mouse. No more than five trials were rejected from any mouse that was included in the study. Average waves were created from 25 msec prior to stimulus onset until 250 msec post stimulus. All recordings were performed within the animal's home cage, which was placed in a Faraday cage 15 min prior to stimulus onset.

Analyses

Baseline Behavior and EEG Power

Mice were observed for changes in behavior following ketamine. We also performed power spectral analyses using Fast Fourier Transform (FFT) using a bin size of 3.2 Hz between 0 and 60 Hz, to evaluate for changes in EEG power at baseline.

N40 Frequency Response

Previous studies have utilized a variety of frequency ranges to elicit deviance-related components in rodent ERPs (Umbricht et al., 2005; Siegel et al., 2003; Ehlers & Somes, 2002). Because this study employs a new method to elicit deviance-related ERPs, we began by determining whether the amplitude of the N40 was similar in DBA/2 mice across the entire frequency range. Therefore, we measured the amplitude of the N40 to pure tones between 4 and 10 kHz in DBA/2 mice (n = 19). This was

done to ensure that ERP changes following deviant tones were not due to frequency-selective hearing loss. The trial consisted of trains of 40 pure tones with a 500-msec interstimulus interval presented in 2-kHz intervals between 4 and 10 kHz. The amplitude of the N40 (most negative deflection between 25 and 50 msec) was then analyzed for each frequency. This approach follows previous studies that utilize the human N100 to assess hearing for individual frequencies (Hyde, 1997). A repeated measures analysis of variance (rmANOVA) was used to evaluate for differences in N40 amplitude across the frequency range.

P20 Amplitude

A previous study from our group found changes in the amplitude of the P20 following ketamine administration in DBA/2 mice (Maxwell, Ehrlichman, Liang, Trief, et al., 2006). Therefore, we analyzed the amplitude of the P20 (most positive deflection between 10 and 30 msec) for changes following ketamine administration and deviant presentation.

N40 Amplitude and Latency

We analyzed the N40 amplitude to determine if there are deviance-related changes similar to those associated with the human N100. The N40 was recorded for deviant and standard waveforms following vehicle or ketamine. Additionally, the latency of the N40 peak was evaluated within each mouse. The data were analyzed using rmANOVA as previously described with drug condition (saline or ketamine) and stimulus condition (standard or deviant) as within-subject repeated measures (Statistica, Statsoft, Tulsa, OK) (Connolly et al., 2003, 2004; Maxwell, Liang, et al., 2004; Siegel et al., 2003).

Epoch Analysis

Following the method of Umbricht et al. (2005), we divided the average ERP from each mouse into 25-msec bins between 0 and 250 msec for a total of 10 sequential epochs. We then calculated the area of the difference wave (deviant minus standard) for each epoch prior to and following ketamine administration in order to determine if any of these 25-msec temporal epochs exhibited a pitch deviance evoked response. Using this approach, a value of zero for the difference wave within an epoch indicates that there was no deviance-elicited change. The difference waves for each treatment condition were compared against a value of zero using a *t* test to determine if any regions displayed a significant deviance response. We then compared the responses prior to and following ketamine administration to each other using the rmANOVA to determine whether ketamine disrupted any deviance-elicited changes that occurred. Our a priori hypothesis was that a deviance-elicited response should occur immediately following the N40, which would occur in the epoch between 50 and 75 msec (Figure 1, proposed region of late N40 negativity = $\text{Area}_{50–75}$ msec Deviant − $\text{Area}_{50–75}$ msec Standard). This hypothesis follows a series of studies in our group and elsewhere that indicate that all components in mice occur at 40% of the latency in humans (Maxwell, Ehrlichman, Liang, Gettes, et al., 2006; Maxwell, Liang, et al., 2004; Umbricht et al., 2004; Connolly et al., 2003; Siegel et al., 2003). Data were evaluated using an rmANOVA as described above.

RESULTS

Ketamine Increases Low-frequency EEG Power without Overt Behavioral Changes

There were no qualitative changes in locomotor activity, stereotypies, grooming, or ataxia following ketamine (10 mg/kg), either at rest or when being handled. FFT analyses between 0 and 60 Hz indicate that ketamine caused an increase in power between 0 and 9.8 Hz (0–3.2, $p < .01$; 3.3–6.5, $p < .01$; 6.6–9.8, $p < .02$). There were no significant changes in any frequency band above 9.8 Hz following ketamine. This increase in low-frequency EEG activity at baseline suggests that mice may have a reduced level of arousal following 10 mg/kg ketamine.

Baseline Responses are Equal across the 4–10 kHz Frequency Range

Prior to assessing pitch deviance detection in mice, we evaluated frequency-specific responses to ensure that all frequencies used in the deviance detection task yielded similar N40 amplitude when presented alone. Subsequently, the deviance detection task was presented prior to and following ketamine administration in order to determine whether ketamine treatment leads to deficits in pitch deviance processing in mice that resemble those in schizophrenia. The amplitude of the N40 did not differ with stimulus frequency between 4 and 10 kHz [$F(3, 54) = .442, p = .7$], indicating that there is no difference in baseline ERP response across this range of stimuli (Table 1). Therefore, this range was selected for subsequent studies of pitch deviance detection.

No Effect of Deviance or Ketamine on the Amplitude of the P20

The NMDA receptor antagonist ketamine was administered to model ERP deficits similar to those seen in schizophrenia. There were no main effects of ketamine [$F(1, 7) = 0.08, p = .8$] or stimulus condition [$F(1, 7) = 0.05, p = .8$] on the amplitude of the P20. Additionally, there was no significant interaction between ketamine

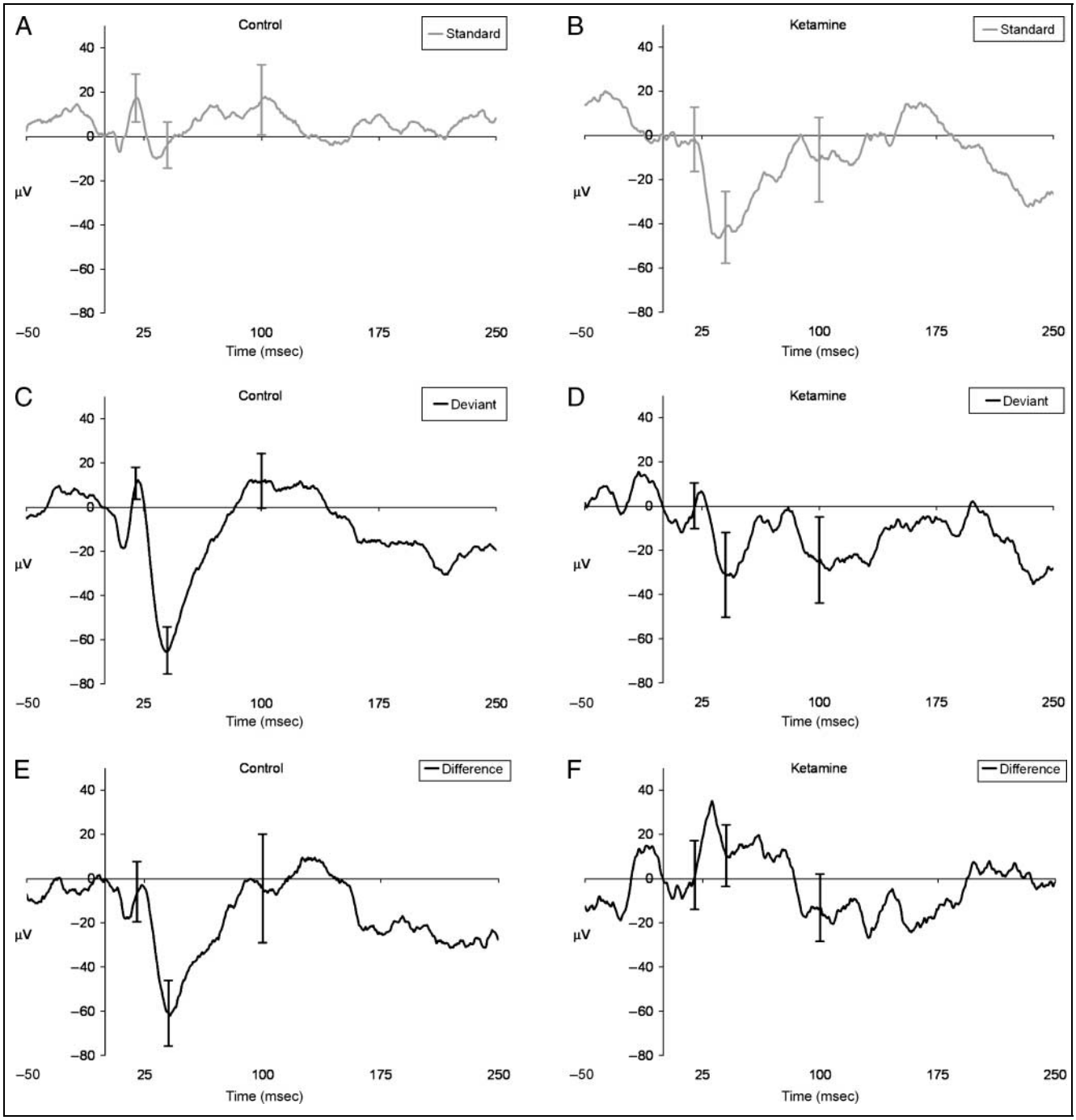

Figure 1. Grand-average ERPs: The grand-average waveform in response to standard (gray) and deviant (black) stimuli for control (A and C) and 10 mg/kg ketamine (B and D). The difference in area (deviant − standard) is represented by waveforms for (E) control and (F) 10 mg/kg ketamine. The error bars in each waveform indicate the mean ± *SEM* at 20, 40, and 100 msec.

and stimulus condition [$F(1, 7) = 0.07, p = .8$], indicating that neither had any effect on the P20.

Effect of Deviance on the Amplitude of the N40 is Attenuated by Ketamine

There were no main effects of ketamine [$F(1, 7) = 0.76$, $p = .4$] or stimulus condition [$F(1, 7) = 3.31, p = .1$] on the amplitude of the N40. However, there was a significant interaction between ketamine and stimulus condition [$F(1, 7) = 6.60, p = .037$], suggesting that ketamine alters the effect of deviance on N40 amplitude as shown in Figure 2. Post hoc analyses (Fisher's LSD MS = 1545.4, $df = 7$) show that the N40 amplitude is increased following the deviant stimulus in the control condition ($p < .038$), but that ketamine disrupted this effect (standard

Table 1. DBA2/Hsd Mice Have Similar Amplitude of N40 Auditory Responses between 4 and 10 kHz

Frequency (kHz)	*Mean ± SEM*
4	−48.87 ± 9.31
6	−40.82 ± 7.92
8	−45.23 ± 10.57
10	−51.87 ± 8.94

The mean amplitudes ± *SEM* for the N40 at 4, 6, 8, and 10 kHz frequency range are shown.

There were no significant differences for N40 response between any of the frequencies, indicating that all frequencies in this range generate similar amplitude N40 in DBA/2 mice.

vs. deviant, $p = .3$). Furthermore, ketamine caused a significant increase in the amplitude of the standard N40 response ($p < .036$). The standard response following ketamine resembled the deviant response following saline, suggesting that ketamine disrupted the ability to establish echoic memory for repeated stimuli (standard post ketamine vs. deviant post saline, $p < 1.0$).

Latency of the N40 is Increased by Ketamine

The N40 reached its peak amplitude at a later time point following ketamine when compared to the saline trials [$F(1, 7) = 5.64$, $p < .05$]. There was no change in the latency of response between the standard and deviant stimuli [$F(1, 7) = 3.18$, $p = .1$] nor any interaction of drug and stimulus conditions [$F(1, 7) = 0.06$, $p = .8$]. Therefore, ketamine increased latency of the N40 response across all auditory stimuli (Figure 3).

Epoch Analysis Indicates an Effect of Deviance that is Attenuated by Ketamine

Three epochs (25–50, 50–75, and 200–225 msec) were significantly different than zero for the deviant − standard conditions following vehicle, but no differences were found for the ketamine condition (Table 2). In the rmANOVA comparing the difference values (deviant − standard) following saline versus ketamine, there was no main effect of drug condition [$F(1, 7) = 0.52$, $p = .5$] or temporal epoch [$F(9, 63) = 0.17$, $p < 1.0$]. However, there was a significant interaction between drug condition and temporal epoch [$F(9, 63) = 2.7708$, $p < .010$] that indicates a difference for deviance values prior to and follow ketamine administration within only two specific epochs. Post hoc analyses (Fisher's LSD MS = 1816E3, $df = 63$) revealed that only the 25–50 and 50–75 msec epochs differed significantly ($p < .001$ and $p < .010$, respectively) between the saline and ketamine trials (Figure 4).

We then evaluated the two regions that showed deviance-related changes that were attenuated by ketamine to determine whether the effects of ketamine were manifest on the standard or the deviant. Therefore, these two temporal regions were evaluated for the effects of both stimulus conditions (standard and deviant) and ketamine using the rmANOVA. The area between 25 and 50 msec had no main effect of stimulus condition [$F(1, 7) = 2.48$, $p = .2$] or ketamine [$F(1, 7) = 0.98$, $p = .8$]. There was a significant interaction between the

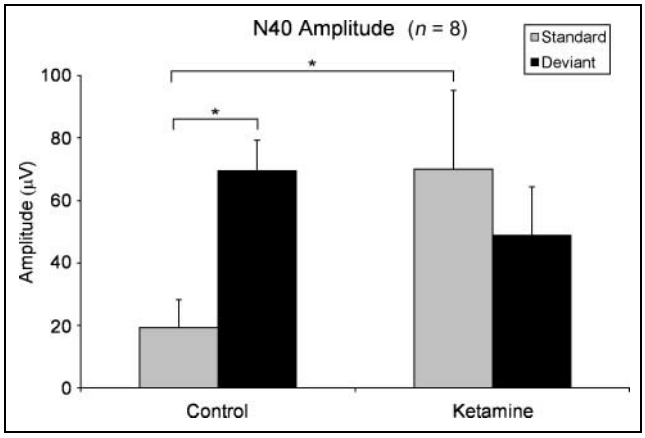

Figure 2. Ketamine increased N40 amplitude to standard tones and blocked augmentation of deviance-elicited N40: The amplitude of the N40 was significantly increased for the deviant tone (black) relative to the standard (gray) in the control condition. However, there was no significant difference between the N40 to standards and deviants following ketamine. Note that the deviant response in the saline condition was not significantly different than either the standard or deviant response after ketamine. These data suggest that the loss of deviance detection following NMDA receptor antagonism may be due to a reduction in the ability to establish echoic memory for the standard stimulus. Data are presented as mean ± *SEM*. *$p < .05$ (Fisher's LSD post hoc test).

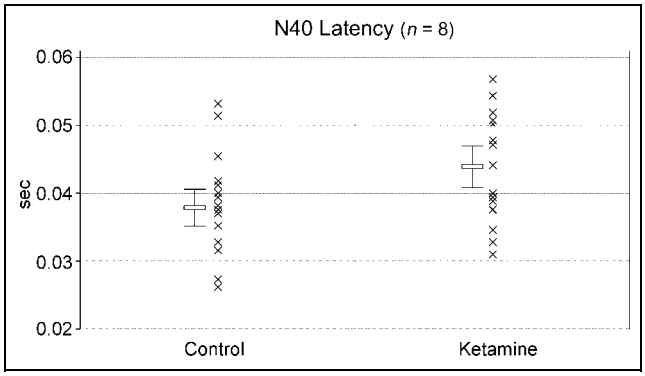

Figure 3. Ketamine increases N40 latency: Scatterplot of N40 peak latencies in each mouse for both treatment conditions are shown. The latency of the N40 following 10 mg/kg ketamine was significantly increased relative to the control condition. These data support an effect of ketamine that causes increased processing time, perhaps due to reduced neuronal synchrony. The mean is designated by the rectangle and the error bars indicate standard error of the mean (±*SEM*).

Table 2. Initial Epoch Analysis Indicates an Effect of Deviance

Epoch (msec)	*Mean ± SEM*	*p*
0–25	−349.70 ± 339.8	.3
25–50	−1844.97 ± 561.6	**.013**
50–75	−1397.03 ± 515.3	**.030**
75–100	−265.06 ± 886.2	.8
100–125	−67.48 ± 888.8	.9
125–150	221.54 ± 624.1	.7
150–175	−668.23 ± 502.9	.2
175–200	−928.35 ± 436.5	.1
200–225	−1133.32 ± 157.1	**< .001**
225–250	−1175.62 ± 594.2	.1

The mean area ± *SEM* for each 25 msec epoch from 0 to 250 msec of the difference wave (deviant − standard) for the saline condition are shown.

Statistical values are from *t* test comparisons of each epoch to zero.

stimulus and ketamine conditions [$F(1, 7) = 6.39, p = .039$] that indicated a difference in response to the standard and deviant tones following ketamine when compared to saline. Post hoc analyses (Fisher LSD MS = 2234E3, $df = 7$) show an increase in the response to deviant stimuli ($p < .045$) compared to the standard stimuli prior to but not following ketamine administration ($p = .3$). For the 50–75 msec region, neither ketamine [$F(1, 7) = 0.60, p = .5$] nor stimulus condition (standard or deviant) [$F(1, 7) = 1.62, p = .2$] resulted in an independent change in area within the proposed late N40 negativity window. Similar to the preceding region, a significant interaction between the stimulus and ketamine conditions [$F(1, 7) = 7.21, p = .031$] revealed an enlargement of the area in response to deviant stimuli following vehicle but not ketamine (Figure 5). These data indicate that there is a response following the N40 between 50 and 75 msec to deviant stimuli under control conditions but that ketamine blocks this effect. Post hoc analyses (Fisher's LSD MS = 1027E3, $df = 7$) further show that ketamine caused a significant increase in the area for the standard ($p < .030$), and a nonsignificant decrease in area for the deviant ($p = .3$) that eliminated the difference between them in this temporal window ($p = .031$ for vehicle, $p = .3$ for ketamine). This finding suggests that ketamine both disrupts the normal establishment of standard responses as well as reducing the difference in response between standard and deviant. Overall, ketamine significantly increased the amplitude of the N40 as well as the subsequent temporal region in response to standard stimuli.

DISCUSSION

The current study describes pitch deviance-elicited changes in the mouse N40 and subsequent temporal region between 50 and 75 msec, corresponding to a late N40 negativity. Furthermore, both of these responses were attenuated by ketamine. A great deal of effort has focused on determining the role of various circuits and neurotransmitters in human N100 and MMN deficits because of the proposed consequences of impaired deviance detection and to guide future treatments. Toward this end, changes in the N100 and MMN have been associated with NMDA receptor-mediated glutamate neurotransmission such that NMDA receptor antagonists reduce N100 in humans and N40 in mice as well as MMN in both humans and monkeys (Maxwell, Ehrlichman, Liang, Trief, et al., 2006; Murck, Spitznagel, Ploch, Seibel, & Schaffler, 2005; Umbricht et al., 2002; Javitt, Jayachandra, et al., 2000). Additionally, NMDA receptor antagonist-mediated disruption of MMN has been proposed as a predictive biomarker for sensitivity to psychosis based on the subjective

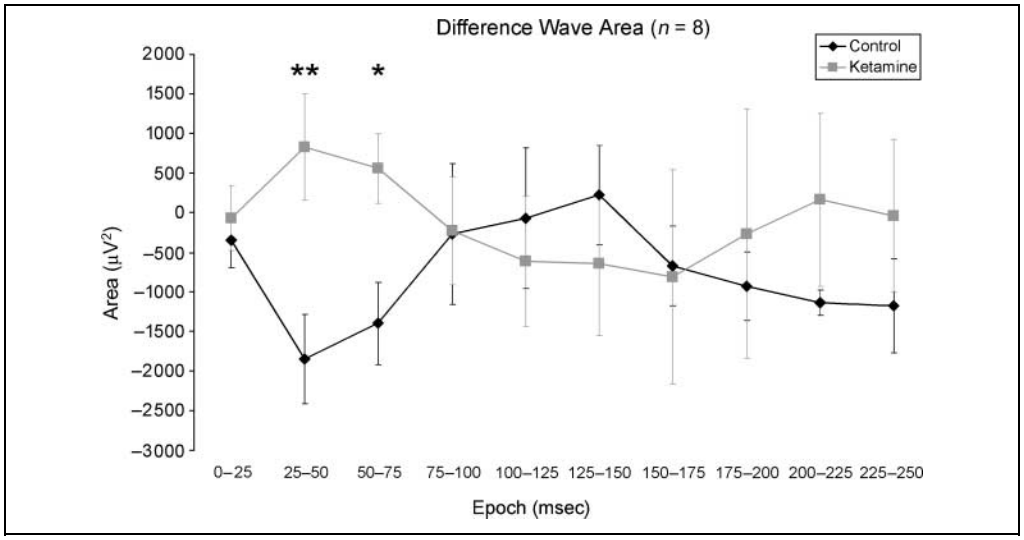

Figure 4. Epoch analysis indicates an effect of deviance that is lost following ketamine: The area for each 25-msec epoch of the difference wave (deviant − standard) in the saline (black) and ketamine (gray) conditions. There was a significant difference between saline and ketamine condition for the second (25–50 msec) and third (50–75 msec) epoch. Data are presented as mean ± *SEM*. *$p < .01$, **$p < .001$.

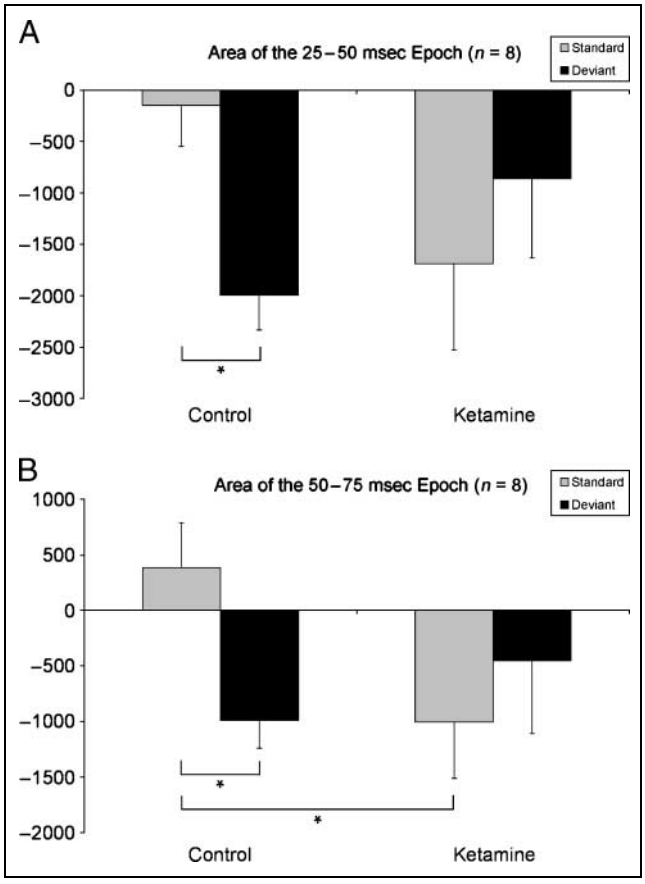

Figure 5. Deviance-elicited changes in the area are abolished by ketamine: The area of the 25–50 msec epoch (A) and 50–75 msec epoch (B) was significantly increased for the deviant tone (black) relative to the standard (gray) in the control condition. However, there was no significant difference between the area in response to standards and deviants following 10 mg/kg ketamine. Similar to the amplitude in Figure 2, the deviant response in the control condition was not significantly different than either the standard or deviant response after ketamine. These data support the hypothesis that there is a loss of deviance detection following NMDA receptor antagonism, which may reflect impaired ability to establish echoic memory for the standard stimulus. Data are presented as mean ± *SEM*. *$p < .05$ (Fisher's LSD post hoc test).

experiences of humans following use of NMDA receptor antagonist drugs of abuse (Umbricht et al., 2002).

The finding of an enhanced N40 following deviant stimuli is in agreement with previous work that has shown similar changes in the human N100 (Brown et al., 2000; Escera, Alho, Winkler, & Näätänen, 1998; van Hooff, de Beer, Brunia, Cluitmans, & Korsten, 1997). One concern when studying frequency deviance response is the tendency of the N100 to increase in size as the pitch of the stimuli increases, regardless of standard or deviant character, also known as the N1 effect. In order to control for the N1 effect, we first checked the amplitude of N1 response across the entire frequency range used, 4–10 kHz. Second, we created a deviance paradigm such that the mean frequency of the standard and deviant stimuli was equal within every trial.

There are several implications and limitations to the current work. The observation that the N40 amplitude increases in response to deviant stimuli provides further support that the mouse N40 auditory ERP shares analogy with the human N100 for a variety of stimulus and pharmacological response properties (Maxwell, Ehrlichman, Liang, Gettes, et al., 2006; Siegel et al., 2005; Maxwell, Liang, et al., 2004; Ehlers & Somes, 2002; Javitt, Jayachandra, et al., 2000; Shelley et al., 1999; Adler, Hoffer, Wiser, & Freedman, 1993; Adler, Rose, & Freedman, 1986). However, the close temporal relationship between the human N100 and MMN components often leads to overlapping waveforms and difficulties in distinguishing one from the other (Näätänen, Simpson, & Loveless, 1982). Similarly, it is difficult to determine if the changes within the 25–50 and 50–75 msec windows are a unitary phenomenon or a continuum of sequential processes. Regardless of whether the deviance-related change in N100 and MMN reflect distinct processes or a continuum of related alterations, people with schizophrenia show deficits in the ability to encode change in the auditory environment across these components (Michie, 2001; Winterer et al., 2001; Brown et al., 2000; Javitt, Jayachandra, et al., 2000; Laurent et al., 1999; Shelley et al., 1999; Catts et al., 1995; Javitt et al., 1993). Similar to reports in humans, changes in the mouse N40 response may mask the generation of an independent negative component. Thus, one interpretation of our data is that the latency window for a late N40 negativity response in mouse is between 50 and 75 msec, immediately following the peak N40 latency. The window for late N40 negativity in mice spans the earlier range of latencies predicted by published data for human MMN (Light & Braff, 2005; Bramon et al., 2004; Näätänen, Pakarinen, Rinne, & Takegata, 2004; Umbricht et al., 2002; Brown et al., 2000; Näätänen & Winkler, 1999; Ruusuvirta, 1999; Shelley et al., 1999). This hypothesis is also based on previous findings that ERP component latencies in mice correspond to 40% of the latencies in human (Maxwell, Ehrlichman, Liang, Gettes, et al., 2006; Umbricht et al., 2004, 2005; Connolly et al., 2004; Maxwell, Liang, et al., 2004; Siegel et al., 2003). Therefore, we propose that this paradigm can be used as a measure of early deviance-related activity in mice.

The MMN has been previously suggested to reflect primary cortical sensory memory (Haenschel et al., 2005; Umbricht et al., 2000, 2005; Javitt et al., 1996, 1998; Kropotov et al., 1995). This theory proposes that qualitative features of each stimulus, such as pitch or duration, are encoded and briefly stored in primary cortical areas to form an echoic trace memory that is facilitated by repetition. The MMN is elicited when the qualitative features of a deviant tone fail to match the pattern of the previous series of standard tones (Light & Braff, 2005; Javitt, Shelley, et al., 2000). Therefore, the ability to detect deviance requires the ability to encode and store ''standardness.'' Accordingly, a lack of MMN following a deviant stimulus may result from either a failure to

establish echoic memory to the standard or an inability to detect a deviation from that standard. Our findings suggest that disruption of the deviance response after ketamine results, in part, from an increase in N40 amplitude and generation of a later negative potential to the standard tone without a corresponding increase in these components to the deviant tone. Thus, ketamine disrupted the normal increase in N40 and late N40 negativity components to deviants relative to standard tones. Furthermore, the inability to respond normally to a deviant stimulus may be due to both a lack of deviance detection and impaired formation of standard response.

The observation of increased N40 latency to all stimuli suggests that there may have been a reduction in processing speed and increase in the time to peak synchronous neuronal response following ketamine administration (Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005; Purhonen, Kilpelainen-Lees, Valkonen-Korhonen, Karhu, & Lehtonen, 2005; Squires & Ollo, 1999). Studies in humans have shown a similar increase in latencies of P50 and N100 components in patients with schizophrenia (Louchart-de la Chapelle et al., 2005; Boutros et al., 2004). Together, these findings add further support for the use of ketamine-induced changes in ERPs as an endophenotypic model of schizophrenia.

Changes in arousal level of the mice may lead to differences in the EEG. Therefore, mice are observed for overt changes in behavior following every pharmacological challenge we perform. We have previously studied ketamine at doses of 5, 10, and 20 mg/kg, either given as a single acute injection or as multiple injections over time (Maxwell, Ehrlichman, Liang, Trief, et al., 2006; Connolly et al., 2004; Siegel et al., 2003). There were no observable changes in behavior at the 10-mg/kg dose used in the current study, either at rest or while being handled. Higher doses of 20 mg/kg have been shown to induce motor retardation and ataxia. Alternatively, the FFT power spectral analyses indicated that ketamine caused an increase in low-frequency EEG activity at baseline, suggesting that the mice may have had a reduced level of arousal. It is important to note that there was no main effect of ketamine on N40 amplitude. Rather, only an interaction between ketamine exposure and stimulus deviance was found. This argues against the possibility that our conclusions can best be summarized as a primary effect of arousal on N40.

The N40 and late N40 negativity findings prior to and following ketamine administration support a model of schizophrenia in which ERP abnormalities are related to impaired NMDA receptor-mediated glutamate transmission. The observation that a phenotype in both components can be detected in this group size ($n = 8$ for the latter portion of the study) supports its use in future studies that could incorporate genetic manipulations, where access to large numbers of appropriate subjects can be limiting for subtle behaviors. DBA/2 mice were selected because previous work in our laboratory indicates that they are the most sensitive to ketamine among the strains surveyed (C57BL/6, FVB, C3H/He, DBA/2) in models of sensory gating (Maxwell, Ehrlichman, Liang, Trief, et al., 2006). One limitation to consider when evaluating electrophysiological data, especially while comparing to studies in other laboratories, is the variations that occur in recordings due mainly to differences in electrode location (e.g., skull vs. intracranial) and recording equipment. Additionally, the orientation of brain regions in mouse and human differs with respect to the recording electrode configurations used in each species. Therefore, the resulting dipoles may also differ such that the orientation of specific components may not be the same between species. Furthermore, recent evidence suggests that the observed similarity in ERP patterns between humans and mice may result from earlier components being determined by the fast oscillatory rhythms while the longer latency ones are determined primarily by slower oscillations (Makeig, Debener, Onton, & Delorme, 2004; Anemuller, Sejnowski, & Makeig, 2003; Basar, Schurmann, Demiralp, Basar-Eroglu, & Ademoglu, 2001; Karakas, Erzengin, & Basar, 2000). Although DBA/2 mice have also been proposed as a model for impaired gating of the P20/N40, we propose that this strain is capable of displaying deviance-related changes in ERPs and that these components are attenuated by ketamine (Simosky et al., 2003; Stevens et al., 1998). This finding highlights differences in the underlying mechanisms of deviance detection and gating of evoked potentials. Therefore, the deviance response in mice may provide a complimentary measure of impaired neural function and aid in pharmaceutical target development that is orthogonal to those identified using gating tasks.

In summary, these results support the presence of a pitch deviance-elicited change in N40 amplitude and a subsequent deviance-elicited component between 50 and 75 msec in mice, which displays characteristics similar to those seen with MMN in humans. Furthermore, both of these responses are attenuated by the NMDA receptor antagonist ketamine, supporting the link between deviance detection and the NMDA receptor system. Additionally, these findings are important in the context of demonstrating feasibility to model psychiatric disorders with impaired deviance responses through the future use of pharmacological and genetic manipulations in mice. The observed effects of deviance on the mouse N40 further support the hypothesis that this component is analogous to the human N100.

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