Published in final edited form as:

Dev Neurobiol. 2014 October ; 74(10): 972–986. doi:10.1002/dneu.22175.

Degraded Auditory Processing in a Rat Model of Autism Limits the Speech Representation in Non-primary Auditory Cortex

C.T. Engineer, T.M. Centanni, K.W. Im, M.S. Borland, N.A. Moreno, R.S. Carraway, L.G. Wilson, and M.P. Kilgard

School of Behavioral and Brain Sciences, The University of Texas at Dallas, Richardson, Texas 75080

Abstract

Although individuals with autism are known to have significant communication problems, the cellular mechanisms responsible for impaired communication are poorly understood. Valproic acid (VPA) is an anticonvulsant that is a known risk factor for autism in prenatally exposed children. Prenatal VPA exposure in rats causes numerous neural and behavioral abnormalities that mimic autism. We predicted that VPA exposure may lead to auditory processing impairments which may contribute to the deficits in communication observed in individuals with autism. In this study, we document auditory cortex responses in rats prenatally exposed to VPA. We recorded local field potentials and multiunit responses to speech sounds in primary auditory cortex, anterior auditory field, ventral auditory field, and posterior auditory field in VPA exposed and control rats. Prenatal VPA exposure severely degrades the precise spatiotemporal patterns evoked by speech sounds in secondary, but not primary auditory cortex. This result parallels findings in humans and suggests that secondary auditory fields may be more sensitive to environmental disturbances and may provide insight into possible mechanisms related to auditory deficits in individuals with autism.

Keywords

speech; auditory cortex; autism; valproic acid; neurophysiology

INTRODUCTION

It is estimated that 1 in 88 children in the United States is affected by autism (Baio, 2012). Autism is characterized by deficits in social communication and restricted, repetitive behaviors (Rapin, 1997). Detailed psychophysical studies have shown that autistic individuals are severely impaired in their ability to process the subtle cues used in everyday communication and social interactions (Alcantara et al., 2004; Rapin and Dunn, 2003; Siegal and Blades, 2003).

The abnormal perception of speech sounds appears to exacerbate the communication and social impairments characteristic of autism. Functional imaging studies have confirmed serious deficits in speech sound processing in both children and adults with autism (Boddaert et al., 2004; Bomba and Pang, 2004). Autistic children exhibit impaired processing of speech sounds (Ceponiene et al., 2003; Kuhl et al., 2005; Oram Cardy et al., 2005; Whitehouse and Bishop, 2008). Auditory responses are delayed, weaker, and unreliable in children with autism (Bomba and Pang, 2004; Dinstei et al., 2012; Gandal et al., 2010; Roberts et al., 2011). Autism severity is well correlated with the delayed latency of auditory evoked cortical responses (Russo et al., 2009). Speech sound processing impairments do not improve over time, and are still seen in adults with autism (Bomba and Pang, 2004; Buchwald et al., 1992; Gervais et al., 2004). Although imaging results suggest that the degradation of speech sound responses are responsible for deficits in understanding and producing spoken language (Lai et al., 2012), the great heterogeneity in autism populations and the limited resolution of current imaging methods makes it difficult to precisely document speech evoked neural activity in autism. An animal model would be valuable to test the neural basis of speech sound impairments in autism.

Prenatal exposure to the antiepileptic drug VPA (which is marketed as Depakote, Epilim, and other names) causes a large increase in the risk of autism in children (Christensen et al., 2013; Christianson et al., 1994; Meador and Loring, 2013; Moore et al., 2000; Ornoy, 2009; Rasalam et al., 2005; Williams et al., 2001). The VPA dose during the first trimester is significantly correlated with language outcome. Children prenatally exposed to a larger VPA dose have worse language scores (Meador et al., 2011; Nadebaum et al., 2010, 2011) and lower IQs (Meador et al., 2009), while children prenatally exposed to a smaller VPA dose have better language scores and higher IQs. More than 60% of VPA exposed children require speech therapy or educational support (Adab et al., 2001; Moore et al., 2000; Viinikainen et al., 2006). Prenatal exposure to VPA is a well-validated animal model of autism that mimics many of the classic neural abnormalities and behavioral deficits observed in autism, including brainstem defects, loss of cerebellar and superior olivary complex neurons, serotonergic abnormalities, impaired social interactions, increased repetitive behaviors, enhanced anxiety, locomotor hyper activity, abnormal fear conditioning, lower sensitivity to pain, higher sensitivity to non-painful sensory stimulation, impaired pre-pulse inhibition, and enhanced eye-blink conditioning (Favre et al., 2013; Lukose et al., 2011; Markram et al., 2008; Rouillet et al., 2013; Schneider and Przewlocki, 2005; Schneider et al., 2001). Neural responses in many brain areas, including auditory cortex, in VPA exposed rats are hyperexcitable and hyperplastic (Banerjee et al., 2012; Markram et al., 2008; Rinaldi et al., 2008a,b; Silva et al., 2009). Additionally, delayed auditory responses and reduced gamma band phase locking in auditory cortex have been reported in both autistic children and VPA exposed mice (Gandal et al., 2010). These results provide strong support for the use of prenatal VPA exposure in rats as an animal model of autism (Markram et al., 2007).

It is reasonable to investigate the neural deficits in speech sound processing in rats because the basic neural mechanism used to process speech sounds up to the level of auditory cortex appear to be shared with other mammals. Rats are able to accurately discriminate between English consonant and vowel sounds (Centanni et al., 2013; Engineer et al., 2008,

2013; Porter et al., 2011; Ranasinghe et al., 2012). Importantly, rat behavioral and neural response thresholds to speech in noise, spectrally degraded and temporally degraded speech sound discrimination closely parallel human thresholds (Ranasinghe et al., 2012; Shetake et al., 2011). In this study, we evaluated the precise spatiotemporal firing patterns of auditory cortex neurons in response to speech sounds presented to control rats and rats that were prenatally exposed to VPA. We predicted that VPA exposure would degrade the millisecond precision of speech sounds and reduce or eliminate the neural responses to key acoustic features of human speech (Boddaert et al., 2004; Bomba and Pang, 2004; Engineer et al., 2008; Rinaldi et al., 2008a).

METHODS

Local field potentials and multiunit responses to speech sounds were collected from four auditory cortex fields: primary auditory cortex (A1), anterior auditory field (AAF), ventral auditory field (VAF), and posterior auditory field (PAF). Neural responses from 980 recording sites were recorded in 11 VPA exposed rats and 6 experimentally naïve control rats ($n=476$ and 504, respectively).

Valproic Acid Exposure

Rats were prenatally exposed to VPA on embryonic day 12.5 (E12.5) (Banerjee et al., 2012; Favre et al., 2013; Schneider et al., 2006). Pregnant Sprague-Dawley female rats received a 600 mg/kg sodium valproate intraperitoneal injection. The VPA exposed rats that were used in this study came from seven litters born to seven separate mothers. A maximum of two rats were used from each litter to ensure our results were not litter specific. Pregnant Sprague-Dawley female control rats received an intraperitoneal injection of saline 12.5 days after conception. The VPA and saline injections were often performed at the same time. The saline exposed rats that were used in this study came from four litters born to four separate mothers. Each litter was housed individually until weaning on post-natal day 23, when male and female pups were separated. Male VPA exposed and saline exposed offspring were used for the following experiments. As reported in earlier work, prenatally exposed VPA rats often exhibited crooked tails, undescended testicles, chromodacryorrhea, and digit deformities (Favre et al., 2013; Kim et al., 2013).

Speech Stimuli

The speech sounds presented in this study were identical to the sounds used in many previous studies (Centanni et al., 2013; Engineer et al., 2008, 2014; Perez et al., 2013; Shetake et al., 2011). Each sound was a consonant-vowel-consonant and differed in the initial consonant (“dad” vs. “sad”) or vowel (“dad” vs. “deed”). These sounds were spoken by a female native English speaker. To better match the rat hearing range, the natural speech sounds were frequency shifted one octave higher without altering the amplitude envelope using the STRAIGHT vocoder (Kawahara, 1997). All sounds were calibrated using an ACO-7016 microphone, and the intensity of each speech sound was adjusted so that the loudest 100 ms of the vowel was 60 dB SPL. The set of 11 speech sounds presented during each recording session included the words: “bad,” “dad,” “gad,” “tad,” “sad,” “shad,” “chad,” “deed,” “dud,” “dead,” and “dood.”

Physiology

The recording and surgical procedures used in this study were identical to the procedures used in many previous studies (Centanni et al., 2013; Engineer et al., 2008; Perez et al., 2013). Rats were anesthetized with pentobarbital and held in a custom head holder that did not obstruct the ears. During recordings, a state of areflexia was maintained with supplemental doses of dilute pentobarbital. Heart rate and oxygen saturation were monitored with EKG and pulse oximetry. Recordings were made in a double-walled sound chamber. Action potentials were recorded simultaneously from four Parylene-coated tungsten microelectrodes (1–2 M Ω , FHC) lowered orthogonally into the cortex. Local field potentials (0–300 Hz) were collected from the same electrodes to allow for comparison with spiking data and evoked potentials recorded in humans. During acute physiology experiments, the speaker (TDT FF1) was positioned 90 degrees left of midline to maximally activate contralateral (right) auditory cortex.

Tucker–Davis neurophysiology hardware (RA16 and RX5) and software (SigGen and Brainware) were used for stimulus generation, signal amplification and filtering (0.3 to 8 kHz), and data acquisition. Recordings were made in layers IV and V, and were derived from 50 to 70 recording sites in each animal over the course of each 10–20 h experiment. Penetration sites were chosen to avoid damaging blood vessels while generating a detailed and evenly spaced map. A1 was defined based on its well-defined tonotopy (low to high characteristic frequencies in a posterior to anterior direction) and short latency responses (Kilgard and Merzenich, 1999). AAF was defined based on its well-defined tonotopy (low to high characteristic frequencies in an anterior to posterior direction) and short latency responses (Centanni et al., 2013; Polley et al., 2007). VAF was defined based on its location relative to AAF and A1, lack of defined tonotopy and longer latency responses (Centanni et al., 2013; Polley et al., 2007). PAF was defined based on its proximity to A1, lack of defined tonotopy, and late latency responses (Puckett et al., 2007; Jakkamsetti et al., 2012). Each speech sound was repeated twenty times at each recording site. Tone frequency intensity tuning curves (0–75 dB SPL in 5 dB steps, 1–32 kHz in 0.125 octave steps) were also obtained at every recording site. The interstimulus interval was 2 s for speech sounds and 0.5 s for tones.

Data Analysis

The average number of action potentials in response to speech sounds was quantified using the number of spikes evoked in the first 40 ms of consonant onset. The onset latency was defined as the time point where the response was 3 standard deviations above the spontaneous firing rate. The peak latency was defined as the time point of maximum firing.

Neural classification accuracy was measured using a PSTH-based nearest neighbor classifier to quantify discrimination performance using spike timing from single sweeps of neural activity recorded from rat auditory cortex (Centanni et al., 2013; Engineer et al., 2008; Foffani and Moxon, 2004; Perez et al., 2013; Schnupp et al., 2006). This nearest-neighbor classifier was used to quantify neural discrimination performance based on single trial activity patterns. The response of each single trial was compared with the average activity pattern (PSTH) evoked by each of the speech stimuli presented. The trial currently

considered was not included in the average activity pattern to prevent artifacts. This model assumes that the brain region reading out the information in the spike trials has previously heard each of the sounds nineteen times, and attempts to identify which of the possible choices was most likely to have generated the trial under consideration. Euclidean distance was used to determine the similarity between each single response and the average PSTH generated by each of the sounds. The classifier guessed that the single trial pattern was generated by the sound whose average pattern it most closely resembles (i.e., minimum Euclidean distance). The onset response to each sound was defined as the 40 ms interval beginning when neural activity exceeds the spontaneous firing rate by three standard deviations. This classifier used either precise spike timing information with millisecond precision (40 1-ms bins) or used only the total number of action potentials within the analysis window (1 40-ms bin). Analysis using a nearest-neighbor classifier made it possible to document neural classification based on single trial data.

Vector strength is a measure used to quantify the degree of synchronization between the noise bursts and the neural response, and was computed to compare synchronization between VPA exposed and control rats. The duration of inhibition was quantified as the amount of time between the end of the response to the previous noise burst and the beginning of the response to the next noise burst that was within 2 standard deviations of the spontaneous firing rate.

The threshold, bandwidth, onset latency, and number of driven spikes receptive field properties were quantified for each group using customized MATLAB software (Engineer et al., 2014). The lowest tone intensity that evoked a response for the characteristic frequency at each site was

RESULTS

Cortical Responses to Speech Sounds are Degraded in VPA Exposed Rats

Since individuals with autism often exhibit abnormal auditory evoked responses, we first evaluated auditory evoked responses in our rat model. (Ceponiene et al., 2003; Kuhl et al., 2005; Oram Cardy et al., 2005; Whitehouse and Bishop, 2008). We recorded the local field potentials (LFPs) evoked by speech sounds to determine if prenatal exposure to VPA altered cortical responses in a manner that parallels alterations observed in individuals with autism. Both the N1 and P2 response amplitudes were significantly weaker in AAF in VPA exposed rats compared to control rats [Fig. 1(a)]. The peak to peak N1–P2 amplitude in AAF was 18% smaller in VPA exposed rats ($p < 0.001$, Fig. 2). In A1, the N1 amplitude was stronger in VPA exposed rats compared to controls, leading to a 7% stronger N1–P2 amplitude in VPA exposed rats compared to controls ($p = 0.007$, Fig. 2). The N1–P2 amplitudes in VAF and PAF were not significantly different between VPA exposed and control rats ($p > 0.05$, Fig. 2). The impaired local field potentials to speech sounds in AAF may indicate that the cortical representation of speech sounds is less robust in VPA exposed rats.

To determine if the auditory cortex responses to speech sounds are impaired, we recorded multiunit responses (Figs. 3 and 4). The average number of action potentials in AAF evoked by the set of 11 speech sounds was 43% weaker in VPA exposed rats compared to control

rats ($p < 0.001$, first 40 ms response, Fig. 5). The response strength to speech sounds in each of the other 3 fields was not significantly different between VPA and control rats ($p > 0.05$). In addition to having weaker responses, AAF neurons in VPA rats also responded significantly slower to speech sounds compared to control rats. The AAF onset latency to speech sounds was 9% later in VPA rats compared to control rats [$p = 0.003$, Fig. 6(a)]. The peak latency in AAF was 32% later in VPA rats compared to control rats [$p = 0.01$, Fig. 6(b)]. The onset and peak latencies to speech sounds in each of the other 3 fields was not significantly different between VPA and control rats ($p > 0.05$). The cortical representation of speech sounds in AAF is significantly weaker and delayed in VPA exposed rats.

In experimentally naïve rats, neural similarity predicts behavioral discrimination performance using all four auditory fields (Centanni et al., 2013; Engineer et al., 2008; Perez et al., 2013). Due to the weaker and slower onset responses in AAF of VPA exposed rats, we tested the hypothesis that a classifier using neural activity from each auditory field would be more impaired at consonant discrimination using AAF responses. At each recording site, a nearest-neighbor classifier was used to identify which of two consonant sounds was presented. Classifier performance in AAF was 5% worse in VPA exposed rats compared to control rats [$p = 0.005$, Fig. 7(a), 40 ms response window with 1 ms bins]. Classifier performance was unaltered in A1, VAF, or PAF of VPA exposed rats compared to control rats [$p > 0.05$, Fig. 7(a)].

In contrast to consonants, which rely on spike timing, the neural discrimination of vowels relies on mean spike rate (Perez et al., 2013). Neural discrimination of vowel sounds was unimpaired in all four auditory fields in VPA exposed rats compared to control rats [$p > 0.05$, Fig. 7(b), 300 ms response window with a single 300 ms bin]. These results suggest that consonant discrimination, which relies on precise spike timing, is more affected in VPA exposed rats. Degraded classifier performance could result from less precise temporal processing or from less precise spectral processing.

Cortical Phase Locking is Degraded in VPA Exposed Rats

Previous studies in individuals with autism using repeating non-speech sounds show deficits in temporal processing (Buchwald et al., 1992). To test whether there are temporal processing impairments in VPA exposed rats, responses to a 10 Hz train of noise bursts were recorded in each of the four auditory fields (Fig. 8). Synchronization was 12% reduced in VPA exposed rats compared to control rats in AAF [$p < 0.001$, Fig. 9(a)] and 13% reduced in PAF [$p = 0.04$, Fig. 9(a)], but was unaltered in A1 and VAF ($p > 0.05$). There was no difference in onset latency to the initial noise burst between VPA and control rats in any of the 4 fields tested ($p > 0.05$). The average peak firing rate in response to the noise bursts was 32% reduced in VPA exposed rats compared to control rats in AAF [$p < 0.001$, Fig. 9(b)], 10% reduced in A1 [$p = 0.03$, Fig. 9(b)], and 42% reduced in VAF [$p < 0.001$, Fig. 9(b)]. There was no difference in peak firing rate in PAF in VPA exposed rats compared to control rats [$p = 0.65$, Fig. 9(b)].

The PSTH plots of the response to the noise bursts suggest that AAF in VPA rats was more quickly released from inhibition compared to AAF in naïve control rats [Fig. 8(a)]. This tendency might account for the decrease in peak firing rate to each noise burst. The duration

of post-stimulus suppression of spontaneous activity was quantified for both groups in each field. As suspected, the duration of inhibition in AAF in VPA exposed rats was shorter compared to control rats, and the duration of inhibition decreased with each successive noise burst. For example, after the first noise burst, there was 90 ± 1 ms of inhibition in the control rats and 87 ± 1 ms of inhibition in the VPA exposed rats ($p = 0.23$). After the fifth noise burst, there was still 81 ± 1 ms of inhibition in the control rats, but only 72 ± 2 ms of inhibition in the VPA exposed rats [$p < 0.0001$, Fig. 8(a)]. This finding was specific to AAF; in A1 the duration of inhibition after each noise burst was comparable between control and VPA exposed rats [87 ± 1 vs. 86 ± 1 ms after the first noise burst, $p = 0.54$; and 82 ± 1 vs. 81 ± 1 ms after the fifth noise burst, $p = 0.57$; Fig. 8(b)].

Spectral Processing is Degraded in VPA Exposed Rats

Individuals with autism often have enhanced spectral processing of simple auditory stimuli (pure tones), but degraded spectral processing of spectrally complex auditory stimuli (vowels) (Eaton et al., 2003; Samson et al., 2006). To assess spectral processing ability in VPA rats, we recorded responses to tones presented at 81 frequencies (1–32 kHz) and 16 intensities (0–75 dB). As seen with the speech and noise burst stimuli, AAF neurons were impaired at responding to tone stimuli. Thresholds were 23% increased in AAF in VPA exposed rats compared to control rats ($p = 0.003$, Table 1). Bandwidths computed 40 dB above threshold were 11% wider in AAF ($p = 0.04$), 15% wider in A1 ($p < 0.0001$), and 14% wider in PAF ($p = 0.003$) in VPA exposed rats compared to control rats (Table 1). Onset latency was 34% slower in AAF in VPA exposed rats compared to control rats ($p < 0.0001$, Table 1). The number of driven spikes in response to tones was 50% weaker in VPA exposed rats compared to control rats in AAF ($p < 0.0001$, Table 1), 44% weaker in VAF ($p = 0.03$, Table 1), 75% stronger in PAF ($p < 0.0001$, Table 1), and unimpaired in A1 ($p > 0.05$, Table 1). Overall, A1, VAF, and PAF were relatively unaffected in VPA exposed rats, while AAF responses to tones were significantly impaired.

To further explore spectral processing in VPA exposed rats, tone rate intensity functions were plotted for each auditory field (Fig. 10). Responses to tones in AAF were weaker at intensities between 20 and 65 dB [$p < 0.0031$, Bonferroni's correction, Fig. 10(a)]. As seen with the other stimuli, A1 responses to tones were not significantly different between VPA exposed and naïve control rats [Fig. 10(b)]. Responses to tones in VAF were slightly weaker at mid-intensities [Fig. 10(c)]. Surprisingly, responses to tones in PAF were stronger in VPA exposed rats [Fig. 10(d)].

In addition to basic firing differences, the general organization of the auditory fields was affected by prenatal VPA exposure. A1 and AAF are known to be strongly tonotopic fields (Polley et al., 2007; Puckett et al., 2007). Each individual naïve control rat had a statistically significant correlation between anterior-posterior location and characteristic frequency for both A1 [average R^2 for individual control animals: 0.69 ± 0.03 , $p < 0.05$, Fig. 11(a)] and AAF [average R^2 for individual control animals: 0.54 ± 0.12 , $p < 0.05$, Fig. 11(a)]. Prenatal exposure to VPA reduces the tonotopic organization in AAF. Each individual VPA exposed rat had a statistically significant correlation between anterior-posterior location and characteristic frequency for A1 [average R^2 for individual control animals: 0.64 ± 0.07 , p

<0.05, Fig. 11(b)], however only 40% of VPA exposed animals had a statistically significant correlation between anterior–posterior location and characteristic frequency for AAF [average R^2 for individual control animals: 0.30 ± 0.05 , Fig. 11(b)].

DISCUSSION

Summary of Results

Impaired social communication is a well-known symptom of autism, and the brain responses of autistic individuals to auditory stimuli are often degraded (O'Connor, 2012). In this study, we extend previous findings by examining cortical responses in four auditory fields evoked by both speech and nonspeech sounds in the VPA model of autism. Responses are degraded in rats prenatally exposed to VPA in non-primary auditory cortex, but not primary auditory cortex. Our results are consistent with recent imaging studies showing that individuals with autism have normal A1 activity and connectivity, but reduced responses and connectivity in secondary auditory fields (Abrams et al., 2013; Lai et al., 2011).

Responses to speech sounds are both weaker and delayed in anterior auditory field in VPA exposed rats, but are unimpaired in the other three auditory fields. The differences observed in this animal model may provide insight into possible mechanisms related to auditory deficits in individuals with autism. In contrast, the evoked potential responses to tones in children with autism are varied. Previous studies have reported both shorter and longer latencies and weaker and stronger responses to tone stimuli in children with autism. Responses to tones in VPA exposed rats are both weaker and delayed in anterior auditory field, while responses are stronger in VPA exposed rats than controls in posterior auditory field. The stronger response to tones in posterior auditory field, as well as the stronger N1–P2 response to speech sounds in primary auditory cortex could be related to a compensatory system (in parallel to the weaker responses in other parts of the auditory cortex) or to the enhanced sensory abilities sometimes observed in individuals with autism (Ouimet et al., 2012). This finding that two auditory fields respond differently to tones in VPA exposed rats may be relevant to the inconsistent tone evoked responses observed in children with autism.

The Role of Multiple Auditory Fields

Multiple auditory fields are involved in the transformation of the speech signal (Centanni et al., 2013; Perez et al., 2013; Tsunada et al., 2011). Our results showing a deficit in non-primary, but not primary, auditory cortex are consistent with a recent report that individuals with autism have normal speech evoked responses in A1, but reduced speech evoked responses in the superior temporal gyrus compared to control subjects (Lai et al., 2011). Anatomical and physiological studies have documented the distinct inputs and unique response properties of the different auditory fields. For example, AAF and A1 receive input from two distinct regions of the thalamus that have independent tonotopic axes: the medial ventral division of the medial geniculate and the lateral ventral division of the medial geniculate (Horie et al., 2013). AAF neurons in VPA exposed rats have many basic firing property differences: higher thresholds, wider bandwidths, longer latencies, and weaker spike rates to tones. In contrast, PAF neurons in VPA exposed rats have enhanced spike rates to tones. Neurons in all four auditory fields are impaired at temporal processing. AAF,

A1, and VAF neurons in VPA exposed rats respond more weakly to trains of noise bursts and AAF and PAF neurons are less synchronized. Previous studies have shown that speech sounds evoke unique cortical response patterns in each field (Centanni et al., 2013; Perez et al., 2013). VPA exposure results in weaker and slower responses to speech sounds, which leads to a decreased ability of AAF neurons to discriminate between pairs of speech sounds differing in their initial consonants. Degraded responses in non-primary auditory fields may provide insight into possible mechanisms related to speech processing deficits in autism (Eponen et al., 2003; Lai et al., 2011).

Experimental disruption of AAF has serious consequences on complex sound discrimination. Temporary deactivation of AAF impairs auditory pattern discrimination ability in cats (Lomber and Malhotra, 2008). Lesions of AAF impair the ability of rats to discriminate vowel-like sounds, while lesions of A1, VAF, or PAF do not (Kudoh et al., 2006). In our study, neural discrimination of vowels in AAF was spared, while neural discrimination of consonants was impaired. The neural discrimination of consonants requires precise temporal information, while the neural discrimination of vowels does not (Perez et al., 2013). Since AAF responses to speech were slower in VPA exposed rats, this impacted neural consonant discrimination but not vowel discrimination. These studies support the hypothesis that degraded responses in nonprimary auditory cortex could contribute to speech processing deficits in autism.

Individuals with autism also have abnormal cross-modal interactions which may be related to degraded responses in nonprimary auditory cortex (Martineau et al., 1992; Møller et al., 2005; Reed and McCarthy, 2012). The nonclassical auditory pathway processes inputs from more than one sensory modality and projects directly to nonprimary auditory cortex, while the classical auditory pathway only processes input from a single modality and projects to primary auditory cortex. AAF, which was the most impaired field in our study, has a stronger connection with the dorsal nucleus of the auditory thalamus (Andersen et al., 1980; Phillips and Irvine, 1982), which processes non-classical auditory pathway information. Thus degraded responses in nonprimary auditory cortex could be relevant to multiple auditory processing disturbances in autism.

The VPA Model of Autism

The VPA model of autism captures many important aspects of autism including reduced social interactions and vocalizations in rodents prenatally exposed to VPA (Gandal et al., 2010; Schneider and Przewlocki, 2005). The correlation between degraded prepulse inhibition and degraded gamma band phase locking deficits that is observed in autism is also observed in VPA exposed rodents (Gandal et al., 2010). Language scores and IQ in VPA exposed children are well correlated with the dose of VPA during the first trimester (Meador et al., 2011, 2013; Nadebaum et al., 2010, 2011). Children exposed to a higher dose of VPA have greater language impairments than children exposed to a lower dose of VPA. Behavioral studies are needed to determine whether rats prenatally exposed to VPA exhibit speech discrimination problems, as has been seen in autism (Alcantara et al., 2004; Samson et al., 2006). Based on our neural discrimination of speech sounds result, we predict that VPA exposed rats would be impaired at consonant discrimination. Previous studies have

shown improved auditory responses following intense training in language-learning impaired children (Heim et al., 2013) or drug therapy (Gandal et al., 2010). Additional studies are needed to determine if extensive speech training or drug therapy can improve cortical responses to speech in VPA exposed rodents. The behavioral and physiological richness of speech sound processing could be used to provide a rigorous test of the efficacy of potential therapies.

In summary, VPA exposure in rodents results in speech processing deficits in nonprimary auditory cortex that parallel observations in autism and may provide insight into possible mechanisms related to the known communication deficits in children exposed to VPA. It is possible that speech processing deficits in nonprimary auditory cortex represent a common feature of autism that can arise from multiple causes.

Acknowledgments

Contract grant sponsor: National Institutes of Health; contract grant number: R01DC010433.

Contract grant sponsor: American Speech-Language-Hearing Foundation (Research Grant for New Investigators).

The authors would like to thank WA Vrana, JR Riley, JD Seale, KG Ranasinghe, AC Reed, and EP Buell for assistance with recording sessions, and SA Hays for suggestions on earlier versions of the manuscript.

References

- Abrams DA, Lynch CJ, Cheng KM, Phillips J, Supekar K, Ryali S, Uddin LQ, et al. Underconnectivity between voice-selective cortex and reward circuitry in children with autism. *Proc Natl Acad Sci*. 2013; 110:12060–12065. [PubMed: 23776244]
- Adab N, Jacoby A, Smith D, Chadwick D. Additional educational needs in children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry*. 2001; 70:15–21. [PubMed: 11118242]
- Alcantara JJ, Weisblatt EJ, Moore BC, Bolton PF. Speech-in-noise perception in high-functioning individuals with autism or Asperger's syndrome. *J Child Psychol Psychiatry Allied Discip*. 2004; 45:1107–14.
- Andersen RA, Knight PL, Merzenich MM. The thalamocortical and corticothalamic connections of AI, AII, and the anterior auditory field (AAF) in the cat: Evidence of two largely segregated systems of connections. *J Comp Neurol*. 1980; 194:663–701. [PubMed: 7451688]
- Baio, J. Morbidity and Mortality Weekly Report. Surveillance Summaries. Vol. 61. Centers for Disease Control and Prevention; 2012. Prevalence of Autism Spectrum Disorders: Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008.
- Banerjee A, García-Oscos F, Roychowdhury S, Galindo LC, Hall S, Kilgard MP, Atzori M. Impairment of cortical GABAergic synaptic transmission in an environmental rat model of autism. *Int J Neuropsychopharmacol*. 2012; 1:1–10.
- Boddaert N, Chabane N, Belin P, Bourgeois M, Royer V, Barthelemy C, Mouren-Simeoni MC, et al. Perception of complex sounds in autism: Abnormal auditory cortical processing in children. *Am J Psychiatry*. 2004; 161:2117–2120. [PubMed: 15514415]
- Bomba MD, Pang EW. Cortical auditory evoked potentials in autism: A review. *Int J Psychophysiol*. 2004; 53:161–169. [PubMed: 15246670]
- Buchwald JS, Erwin R, Van Lancker D, Guthrie D, Schwafel J, Tanguay P. Midlatency auditory evoked responses: P1 abnormalities in adult autistic subjects. *Electroencephalogr Clin Neurophysiol Evok Potent Sect*. 1992; 84:164–171.
- Centanni TM, Engineer CT, Kilgard MP. Cortical speech-evoked response patterns in multiple auditory fields are correlated with behavioral discrimination ability. *J Neurophysiol*. 2013; 110:177–189. [PubMed: 23596332]

- eponien R, Lepistö T, Shestakova A, Vanhala R, Alku P, Näätänen R, Yaguchi K. Speech-sound-selective auditory impairment in children with autism: They can perceive but do not attend. *Proc Natl Acad Sci*. 2003; 100:5567–5572. [PubMed: 12702776]
- Ceponiene R, Lepistö T, Shestakova A, Vanhala R, Alku P, Naatanen R, Yaguchi. Speech-sound-selective auditory impairment in children with autism: They can perceive but do not attend. *Proc Natl Acad Sci USA*. 2003; 100:5567–5572. [PubMed: 12702776]
- Christensen J, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, Vestergaard M. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA*. 2013; 309:1696–1703. [PubMed: 23613074]
- Christianson AL, Chesler N, Kromberg JG. Fetal valproate syndrome: Clinical and neuro-developmental features in two sibling pairs. *Dev Med Child Neurol*. 1994; 36:361–369. [PubMed: 7512516]
- Dinstein I, Heeger DJ, Lorenzi L, Minshew NJ, Malach R, Behrmann M. Unreliable evoked responses in autism. *Neuron*. 2012; 75:981–991. [PubMed: 22998867]
- Engineer CT, Perez CA, Carraway RS, Chang KQ, Roland JL, Kilgard MP. Speech training alters tone frequency tuning in rat primary auditory cortex. *Behav Brain Res*. 2014; 258:166–178. [PubMed: 24344364]
- Engineer CT, Perez CA, Carraway RS, Chang KQ, Roland JL, Sloan AM, Kilgard MP. Similarity of cortical activity patterns predicts generalization behavior. *PLoS ONE*. 2013; 8:e78607. [PubMed: 24147140]
- Engineer CT, Perez CA, Chen YH, Carraway RS, Reed AC, Shetake JA, Jakkamsetti V, et al. Cortical activity patterns predict speech discrimination ability. *Nat Neurosci*. 2008; 11:603–608. [PubMed: 18425123]
- Favre MR, Barkat TR, LaMendola D, Khazen G, Markram H, Markram K. General developmental health in the VPA-rat model of autism. *Front Behav Neurosci*. 2013; 7:88.10.3389/fnbeh.2013.00088 [PubMed: 23898245]
- Foffani G, Moxon KA. PSTH-based classification of sensory stimuli using ensembles of single neurons. *J Neurosci Methods*. 2004; 135:107–120. [PubMed: 15020095]
- Gandal MJ, Edgar JC, Ehrlichman RS, Mehta M, Roberts TP, Siegel SJ. Validating γ oscillations and delayed auditory responses as translational biomarkers of autism. *Biol Psychiatry*. 2010; 68:1100–1106. [PubMed: 21130222]
- Gervais H, Belin P, Boddaert N, Leboyer M, Coez A, Sfaello I, Barthelemy C, et al. Abnormal cortical voice processing in autism. *Nat Neurosci*. 2004; 7:801–802. [PubMed: 15258587]
- Heim S, Keil A, Choudhury N, Thomas Friedman J, Benasich AA. Early gamma oscillations during rapid auditory processing in children with a language-learning impairment: Changes in neural mass activity after training. *Neuropsychologia*. 2013; 51:990–1001. [PubMed: 23352997]
- Horie M, Tsukano H, Hishida R, Takebayashi H, Shibuki K. Dual compartments of the ventral division of the medial geniculate body projecting to the core region of the auditory cortex in C57BL/6 mice. *Neurosci Res*. 2013; 76:207–212. [PubMed: 23692741]
- Jakkamsetti V, Chang KQ, Kilgard MP. Reorganization in processing of spectral and temporal input in the rat posterior auditory field induced by environmental enrichment. *J Neurophysiol*. 2012; 107:1457–1475. [PubMed: 22131375]
- Kawahara H. Speech representation and transformation using adaptive interpolation of weighted spectrum: Vocoder revisited. *Proc ICASSP*. 1997; 2:1303–1306.
- Kilgard MP, Merzenich MM. Distributed representation of spectral and temporal information in rat primary auditory cortex. *Hear Res*. 1999; 134:16–28. [PubMed: 10452372]
- Kim KC, Kim P, Go HS, Choi CS, Park JH, Kim HJ, Jeon SJ, et al. Male specific alteration in excitatory post synaptic development and social interaction in prenatal valproic acid exposure model of autism spectrum disorder. *J Neurochem*. 2013; 124:832–843. [PubMed: 23311691]
- Kudoh M, Nakayama Y, Hishida R, Shibuki K. Requirement of the auditory association cortex for discrimination of vowel-like sounds in rats. *Neuroreport*. 2006; 17:1761–1766. [PubMed: 17164660]

- Kuhl PK, Coffey-Corina S, Padden D, Dawson G. Links between social and linguistic processing of speech in preschool children with autism: Behavioral and electrophysiological measures. *Dev Sci*. 2005; 8:F1–F12. [PubMed: 15647058]
- Lai G, Pantazatos SP, Schneider H, Hirsch J. Neural systems for speech and song in autism. *Brain*. 2012; 135:961–975. [PubMed: 22298195]
- Lai G, Schneider HD, Schwarzenberger JC, Hirsch J. Speech stimulation during functional MR imaging as a potential indicator of autism. *Radiology*. 2011; 260:521–530. [PubMed: 21628495]
- Lomber SG, Malhotra S. Double dissociation of ‘what’ and ‘where’ processing in auditory cortex. *Nat Neurosci*. 2008; 11:609–616. [PubMed: 18408717]
- Lukose R, Schmidt E, Wolski TP Jr, Murawski NJ, Kulesza RJ Jr. Malformation of the superior olivary complex in an animal model of autism. *Brain Res*. 2011; 1398:102–112. [PubMed: 21636076]
- Markram H, Rinaldi T, Markram K. The intense world syndrome—An alternative hypothesis for autism. *Front Neurosci*. 2007; 1:77–96. [PubMed: 18982120]
- Markram K, Rinaldi T, La Mendola D, Sandi C, Markram H. Abnormal fear conditioning and amygdala processing in an animal model of autism. *Neuropsychopharmacology*. 2008; 33:901–912. [PubMed: 17507914]
- Martineau J, Roux S, Adrien J, Garreau B, Barthélemy C, Lelord G. Electrophysiological evidence of different abilities to form cross-modal associations in children with autistic behavior. *Electroencephalogr Clin Neurophysiol*. 1992; 82:60–66. [PubMed: 1370145]
- Meador KJ, Loring DW. Risks of *in utero* exposure to valproate. *JAMA*. 2013; 309:1730. [PubMed: 23613078]
- Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): A prospective observational study. *Lancet Neurol*. 2013; 12:244–252. [PubMed: 23352199]
- Meador KJ, Baker GA, Browning N, Cohen MJ, Clayton-Smith J, Kalayjian LA, et al. Foetal antiepileptic drug exposure and verbal versus non-verbal abilities at three years of age. *Brain*. 2011; 134:396–404. [PubMed: 21224309]
- Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, Kalayjian LA, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med*. 2009; 360:1597–1605. [PubMed: 19369666]
- Møller AR, Kern JK, Grannemann B. Are the non-classical auditory pathways involved in autism and PDD? *Neurol Res*. 2005; 27:625–629. [PubMed: 16157013]
- Moore SJ, Turnpenny P, Quinn A, Glover S, Lloyd DJ, Montgomery T, Dean JC. A clinical study of 57 children with fetal anticonvulsant syndromes. *J Med Genet*. 2000; 37:489–497. [PubMed: 10882750]
- Nadebaum C, Anderson V, Vajda F, Reutens D, Barton S, Wood A. Language skills of school-aged children prenatally exposed to antiepileptic drugs. *Neurology*. 2011; 76:719–726. [PubMed: 21339499]
- Nadebaum C, Anderson V, Vajda F, Reutens D, Barton S, Wood A. The Australian brain and cognition and antiepileptic drugs study: IQ in school-aged children exposed to sodium valproate and polytherapy. *J Int Neuropsychol Soc*. 2010; 17:133. [PubMed: 21092354]
- O'Connor K. Auditory processing in autism spectrum disorder: A review. *Neuroscience Biobehav Rev*. 2012; 36:836–854.
- Oram Cardy JE, Flagg EJ, Roberts W, Roberts TP. Delayed mismatch field for speech and non-speech sounds in children with autism. *Neuroreport*. 2005; 16:521–525. [PubMed: 15770164]
- Ornoy A. Valproic acid in pregnancy: How much are we endangering the embryo and fetus? *Reprod Toxicol* (Elmsford, NY). 2009; 28:1–10.
- Perez CA, Engineer CT, Jakkamsetti V, Carraway RS, Perry MS, Kilgard MP. Different timescales for the neural coding of consonant and vowel sounds. *Cereb Cortex*. 2013; 23:670–683. [PubMed: 22426334]
- Phillips D, Irvine D. Properties of single neurons in the anterior auditory field (AAF) of cat cerebral cortex. *Brain Res*. 1982; 248:237–244. [PubMed: 7139275]

- Polley DB, Read HL, Storace DA, Merzenich MM. Multiparametric auditory receptive field organization across five cortical fields in the albino rat. *J Neurophysiol.* 2007; 97:3621–3638. [PubMed: 17376842]
- Porter BA, Rosenthal TR, Ranasinghe KG, Kilgard MP. Discrimination of brief speech sounds is impaired in rats with auditory cortex lesions. *Behav Brain Res.* 2011; 219:68–74. [PubMed: 21167211]
- Puckett AC, Pandya PK, Moucha R, Dai W, Kilgard MP. Plasticity in the rat posterior auditory field following nucleus basalis stimulation. *J Neurophysiol.* 2007; 98:253–265. [PubMed: 17460101]
- Ranasinghe KG, Vrana WA, Matney CJ, Kilgard MP. Neural mechanisms supporting robust discrimination of spectrally and temporally degraded speech. *J Assoc Res Otolaryngol.* 2012; 13:527–542. [PubMed: 22549175]
- Rapin I. Autism. *New Engl J Med.* 1997; 337:97–104. [PubMed: 9211680]
- Rapin I, Dunn M. Update on the language disorders of individuals on the autistic spectrum. *Brain Dev.* 2003; 25:166–172. [PubMed: 12689694]
- Rasalam AD, Hailey H, Williams JH, Moore SJ, Turnpenny PD, Lloyd DJ, Dean JC. Characteristics of fetal anticonvulsant syndrome associated autistic disorder. *Dev Med Child Neurol.* 2005; 47:551–555. [PubMed: 16108456]
- Reed P, McCarthy J. Cross-modal attention-switching is impaired in autism spectrum disorders. *J Autism Dev Disord.* 2012; 42:947–953. [PubMed: 21720723]
- Rinaldi T, Perrodin C, Markram H. Hyper-connectivity and hyper-plasticity in the medial prefrontal cortex in the valproic acid animal model of autism. *Front Neural Circuits.* 2008a; 2:4. [PubMed: 18989389]
- Rinaldi T, Silberberg G, Markram H. Hyperconnectivity of local neocortical microcircuitry induced by prenatal exposure to valproic acid. *Cereb Cortex.* 2008b; 18:763–770. [PubMed: 17638926]
- Roberts TP, Cannon KM, Tavabi K, Blaskey L, Khan SY, Monroe JF, Qasmieh S, et al. Auditory magnetic mismatch field latency: A biomarker for language impairment in autism. *Biol Psychiatry.* 2011; 70:263–269. [PubMed: 21392733]
- Roulet FI, Lai JK, Foster JA. *In utero* exposure to valproic acid and autism—a current review of clinical and animal studies. *Neurotoxicol Teratol.* 2013; 36:47–56. [PubMed: 23395807]
- Russo N, Zecker S, Trommer B, Chen J, Kraus N. Effects of background noise on cortical encoding of speech in autism spectrum disorders. *J Autism Dev Disord.* 2009; 39:1185–1196. [PubMed: 19353261]
- Samson F, Mottron L, Jemel B, Belin P, Ciocca V. Can spectro-temporal complexity explain the autistic pattern of performance on auditory tasks? *J Autism Dev Disord.* 2006; 36:65–76. [PubMed: 16382329]
- Schneider T, Przewlocki R. Behavioral alterations in rats prenatally exposed to valproic acid: animal model of autism. *Neuropsychopharmacology.* 2005; 30:80–89. [PubMed: 15238991]
- Schneider T, Turczak J, Przewlocki R. Environmental enrichment reverses behavioral alterations in rats prenatally exposed to valproic acid: issues for a therapeutic approach in autism. *Neuropsychopharmacology.* 2006; 31:36–46. [PubMed: 15920505]
- Schneider T, Labuz D, Przewlocki R. Nociceptive changes in rats after prenatal exposure to valproic acid. *Polish J Pharmacol.* 2001; 53:531–534.
- Schnupp JW, Hall TM, Kokelaar RF, Ahmed B. Plasticity of temporal pattern codes for vocalization stimuli in primary auditory cortex. *J Neurosci.* 2006; 26:4785–4795. [PubMed: 16672651]
- Shetake JA, Wolf JT, Cheung RJ, Engineer CT, Ram SK, Kilgard MP. Cortical activity patterns predict robust speech discrimination ability in noise. *Eur J Neurosci.* 2011; 34:1823–1838. [PubMed: 22098331]
- Siegal M, Blades M. Language and auditory processing in autism. *Trends Cogn Sci.* 2003; 7:378–380. [PubMed: 12963465]
- Silva GT, Le Be J, Riachi I, Rinaldi T, Markram K, Markram H. Enhanced long term microcircuit plasticity in the valproic acid animal model of autism. *Front Synapt Neurosci.* 2009; 1:1.
- Tsunada J, Lee JH, Cohen YE. Representation of speech categories in the primate auditory cortex. *J Neurophysiol.* 2011; 105:2634–2646. [PubMed: 21346209]

- Viinikainen K, Eriksson K, Monkkonen A, Aikia M, Nieminen P, Heinonen S, Kalviainen R. The effects of valproate exposure in utero on behavior and the need for educational support in school-aged children. *Epilepsy Behav.* 2006; 9:636–640. [PubMed: 17049311]
- Whitehouse AJ, Bishop DV. Do children with autism ‘switch off’ to speech sounds? An investigation using event-related potentials. *Dev Sci.* 2008; 11:516–524. [PubMed: 18576959]
- Williams G, King J, Cunningham M, Stephan M, Kerr B, Hersh JH. Fetal valproate syndrome and autism: Additional evidence of an association. *Dev Med Child Neurol.* 2001; 43:202–206. [PubMed: 11263692]

Figure 1.

VPA exposure altered speech-evoked local field potentials in auditory cortex. (a) The N1 and P2 amplitudes recorded in AAF in response to speech sounds were weaker in VPA exposed rats (red line) compared to naïve control rats (blue line). Gray shading behind each line indicates SEM across recording sites. The black line at the bottom of each subplot indicates time points when VPA exposed rats respond significantly differently than naïve control rats ($p < 0.01$). (b) The N1 amplitude in A1 was significantly larger in VPA exposed rats compared to naïve control rats, while the P2 amplitude was unaltered. (c) Both the N1 and P2 amplitudes were unaltered in VAF in VPA exposed rats compared to naïve control rats. (d) The P2 amplitude in PAF was significantly weaker in VPA exposed rats compared to naïve control rats, while the N1 amplitude was unaltered. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.] defined as the threshold. The range of frequencies that evoke a response in 10 dB increments above the threshold was defined as the bandwidth.

Figure 2.

N1–P2 amplitude in response to speech sounds in VPA exposed and control rats. The N1–P2 amplitude in VPA exposed rats is significantly weaker in AAF, but significantly stronger in A1. Error bars indicate SEM across recording sites.

Figure 3.

Neurograms in response to the speech sound “gad” in control rats (top row) and VPA rats (bottom row) in AAF, A1, VAF, and PAF. Multiunit data was collected from 504 recording sites in 6 anesthetized control rats and 476 recording sites in 11 anesthetized VPA exposed rats. Average poststimulus time histograms (PSTH) derived from 20 repeats were ordered by the characteristic frequency (kHz) of each recording site (y axis). Time is represented on the x axis (–50 to 400 ms). The firing rate of each site is represented in grayscale, where black indicates 400 spikes/s. For comparison, the mean population PSTH evoked by the sound “gad” in each auditory field is plotted above the corresponding neurogram.

Figure 4.

Poststimulus time histograms (PSTHs) in response to the speech sound “gad.” (a) The response to “gad” is weaker in AAF in VPA exposed rats (red line) compared to naïve control rats (blue line). Gray shading behind each line indicates SEM across recording sites. For comparison, the “gad” waveform is plotted in gray above each PSTH. (b) The A1 response to “gad” is largely unaltered in VPA exposed rats compared to naïve control rats. (c) The VAF response to “gad” is weaker in VPA exposed rats compared to naïve control rats. (d) The PAF response to “gad” is largely unaltered in VPA exposed rats compared to naïve control rats. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 5.

Mean spike count in response to speech sounds is decreased in AAF in VPA rats compared to control rats. The number of driven spikes was calculated for the 40 ms onset response. Error bars indicate SEM across recording sites.

Figure 6.

Latency to speech sound response in multiple auditory fields. (a) The onset latency to speech sounds is longer in AAF in VPA rats compared to control rats. Error bars indicate SEM across recording sites. (b) The peak latency to speech sounds is longer in AAF in VPA rats compared to control rats.

Figure 7.

Neural discrimination of consonant and vowel sounds in VPA exposed and control rats. (a) Neural consonant discrimination is impaired in AAF in VPA exposed rats compared to control rats. The classifier used the 40 ms onset response with 1 ms precision to discriminate between pairs of consonants. Error bars indicate SEM across recording sites. Chance performance is 50% correct because discrimination is between two possible choices (two alternative forced choice). (b) Neural vowel discrimination is unaltered in VPA exposed rats compared to control rats. The classifier used the 300 ms mean rate response to the vowel to discriminate between pairs of vowel sounds.

Figure 8.

Post stimulus time histograms (PSTHs) in response to a 10 Hz train of six noise bursts. (a) The response to noise bursts is weaker in AAF in VPA exposed rats (red line) compared to naïve control rats (blue line). Gray shading behind each line indicates SEM across recording sites. (b) The A1 response to noise bursts is largely unaltered in VPA exposed rats compared to naïve control rats. (c) The VAF response to noise bursts is weaker in VPA exposed rats compared to naïve control rats. (d) The PAF response to noise bursts is largely unaltered in VPA exposed rats compared to naïve control rats. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 9.

Cortical phase locking is degraded in VPA exposed rats. (a) The degree of synchronization is decreased in VPA exposed rats (gray bars) compared to naïve control rats (white bars). Error bars indicate SEM across recording sites. (b) The mean peak firing rate across all 6 noise bursts was decreased in AAF, A1, and VAF in VPA exposed rats compared to naïve control rats.

Figure 10.

Tone rate intensity functions for VPA exposed and naïve control rats. (a) VPA rats evoke fewer spikes per tone in AAF compared to control rats. The number of spikes evoked per tone in AAF is plotted at each presented intensity (0–75 dB). Responses to tones within $\frac{1}{2}$ octave of each site's characteristic frequency were averaged together. Error bars indicate s.e.m. across recording sites. Asterisks indicate intensities that are statistically significant between the two groups ($p < 0.0031$, Bonferroni correction). (b) The number of spikes evoked per tone in A1 is comparable between VPA exposed and naïve control rats. (c) The number of spikes evoked per tone in VAF of VPA exposed rats is slightly decreased compared to naïve control rats. (d) The number of spikes evoked per tone in PAF is increased in VPA exposed rats compared to naïve control rats. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 11.

AAF is less tonotopically organized in VPA exposed rats compared to experimentally naïve control rats. Scatterplots of the characteristic frequency versus recording site location for AAF and A1 in (a) naïve control rats and (b) VPA exposed rats. The A1-PAF border for each rat was defined as the most anterior PAF site. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1

Receptive Field Properties of Auditory Cortex Neurons in VPA Exposed and Control Rats

		Thresh (dB)	BW40 (oct)	Onset (ms)	Rate (spikes)
AAF	Naïve	21.7 ±0.9	2.8 ±0.1	14.4 ±0.3	1.6 ±0.1
	VPA	26.6 ±1.4*	3.1 ±0.1*	19.3 ±1.2*	0.8 ±0.1*
A1	Naïve	19.2 ±0.6	2.6 ±0.1	16.0 ±0.3	1.3 ±0.1
	VPA	20.3 ±0.7	3.0 ±0.1*	16.3 ±0.3	1.3 ±0.1
VAF	Naïve	36.1 ±3.3	2.2 ±0.2	17.0 ±1.1	0.9 ±0.2
	VPA	32.1 ±2.3	2.3 ±0.3	19.6 ±2.1	0.5 ±0.1*
PAF	Naïve	24.6 ±1.2	3.6 ±0.1	27.0 ±1.5	0.8 ±0.1
	VPA	21.8 ±1.7	4.1 ±0.1*	31.5 ±2.3	1.4 ±0.1*

Responses are impaired in AAF in VPA exposed rats: the threshold is higher, bandwidth is wider, onset latency is later, and number of driven spikes is lower. Numbers marked with a star are significantly different compared to control rats (* $p < 0.05$).