Auditory Brainstem Responses in an Animal Model of Autism Spectrum Disorder: Audiograms, Sex Differences and Maturation Changes

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Abstract

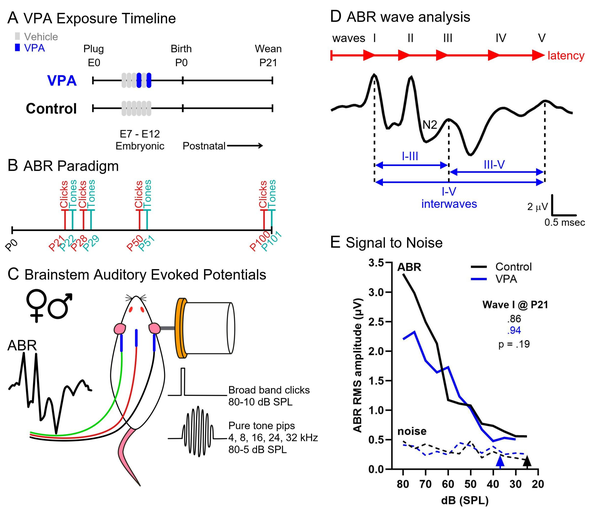
Background: Hearing impairment is an early feature of Autism Spectrum Disorder (ASD), and auditory brainstem response (ABR) abnormalities reflect disrupted neural processing in the auditory brainstem.
Objective: To characterize ABR changes across development and sex in a valproic acid (VPA) model of ASD.
Methods: Rats exposed to VPA *in utero* underwent longitudinal ABR testing (P21–P100) using clicks to assess thresholds, wave latencies, and interwave intervals.
Results: VPA-exposed animals showed persistently elevated thresholds and prolonged absolute and interwave latencies across development, with minimal maturation and no significant sex differences.
Conclusion: *In utero* VPA exposure causes lasting auditory brainstem dysfunction, with wave V latency emerging as a potential biomarker of ASD-related impairment.

Introduction

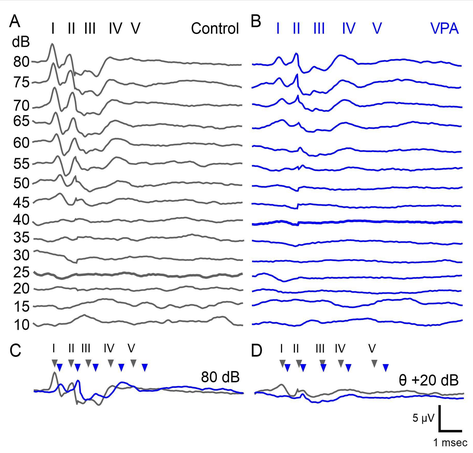
Autism spectrum disorder (ASD) is associated with early auditory dysfunction that can impair language and cognitive development. The auditory brainstem response (ABR) provides a non-invasive measure of neural activity along the ascending auditory pathway and has demonstrated abnormal latency patterns in individuals with ASD. *In utero* exposure to valproic acid (VPA) is a clinically relevant model of ASD that reproduces structural and functional abnormalities of the auditory system.

Method

Pregnant dams were assigned to either a VPA-exposed or control group, with exposed dams receiving peanut butter containing VPA (800 mg/kg) and controls receiving peanut butter alone. Offspring (control vs VPA; male and female) underwent ABR testing at P21, P28, P50, and P100. Click stimuli were used to measure auditory thresholds, wave I–V latencies, and interwave intervals.

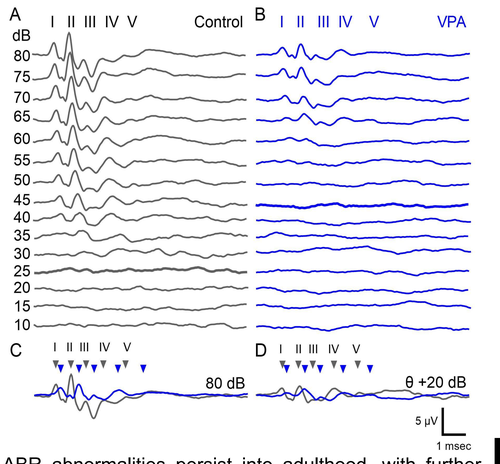


Click-evoked ABRs at P28



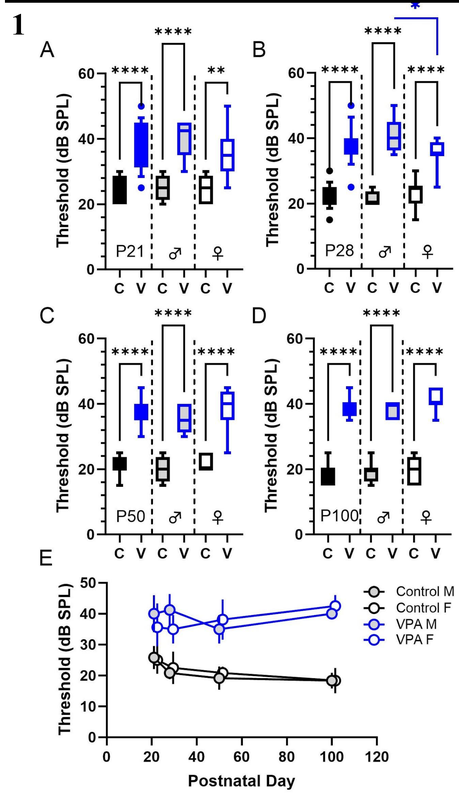
Click-evoked responses show elevated thresholds and altered waveforms in VPA-exposed animals compared to controls. Thresholds are increased (control: 25 dB; VPA: 40 dB), with reduced waveform clarity and delayed peak formation. Comparisons at 80 dB and 20 dB above threshold highlight diminished response amplitude and disrupted wave I–V morphology in VPA animals.

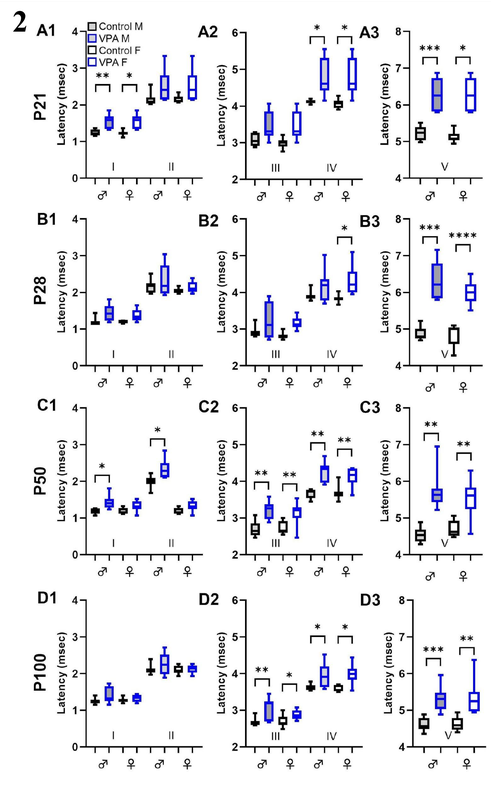
Click-evoked ABRs at P100

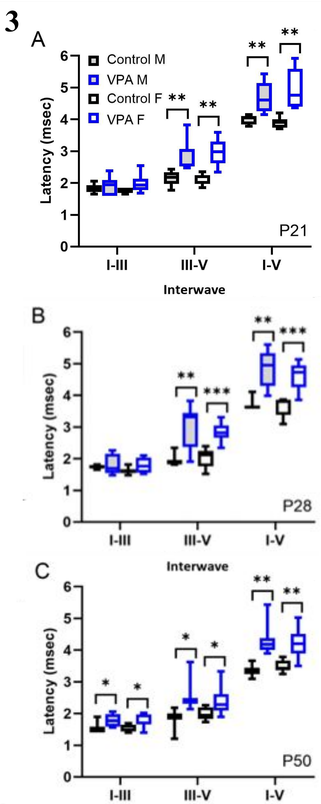


ABR abnormalities persist into adulthood, with further elevated thresholds in VPA-exposed animals (control: 25 dB; VPA: 45 dB). Responses show sustained reductions in waveform clarity and prolonged peak latencies. Comparisons at 80 dB and 20 dB above threshold demonstrate persistent deficits in neural synchrony and auditory brainstem function.

VPA exposed vs controls: thresholds, latencies, interwaves







Across development, VPA-exposed animals exhibit persistent auditory dysfunction characterized by elevated thresholds, prolonged wave latencies, and increased interwave intervals. As shown in Fig 1, VPA-exposed animals demonstrate significantly higher auditory thresholds to broadband clicks at all timepoints (P21–P100), with thresholds remaining elevated (~35–45 dB SPL) compared to controls (~20–25 dB SPL); this difference is consistent across both males and females and is reflected by significant group differences at each timepoint. While control animals show normal maturational improvement in thresholds from P21 to P100, VPA-exposed animals fail to demonstrate comparable improvement, as illustrated in the longitudinal trend (Fig 1E). In Fig 2, absolute wave latency analysis shows consistent prolongation across waves I–V in VPA-exposed animals, with the largest and most significant delays observed in later waves (III–V and V), indicating impaired neural transmission through higher-order brainstem nuclei; these effects are evident at early timepoints (P21–P28) and persist into adulthood (P100), with similar patterns in both sexes. In Fig 3, interwave latency analysis further reveals increased I–III, III–V, and I–V intervals in VPA-exposed animals, particularly at P28 and P50, suggesting disrupted synaptic timing and reduced neural synchrony within the auditory brainstem. Together, these findings demonstrate that *in utero* VPA exposure results in early-onset and long-lasting deficits in auditory sensitivity and brainstem processing that do not normalize with development.

Conclusions

In utero VPA exposure results in persistent auditory dysfunction, evidenced by elevated thresholds, prolonged ABR latencies, and impaired brainstem conduction across development. The absence of normal maturational improvement and consistent delays in later waves indicate disrupted neural processing within the auditory brainstem. These findings demonstrate that VPA exposure produces lasting deficits in auditory sensitivity and central auditory pathway function, supporting its validity as a model of ASD-related auditory impairment. Overall, this study provides evidence that neurodevelopmental disruption from VPA significantly impacts auditory system development and function.