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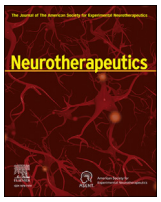

Commentary

Unlock the potential: Auditory-evoked event-related potential (ERP) as a treatment-responsive biomarker for Rett syndrome

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Rett syndrome (RTT) is a progressive X-linked neurodevelopmental disorder (NDD) caused by mutations in the gene encoding methyl-CpG binding protein 2 (MECP2). RTT affects approximately 1 in 10,000 live births and is characterized by normal development for the first 6–18 months followed by developmental stagnation, rapid regression in previously acquired motor, cognitive, and communication skills, breathing difficulties, and seizures [1]. Despite having a known genetic cause, treatment options for RTT have been limited prior to the recent FDA approval of Trofinetide (Daybue), a synthetic analog of glycine-proline-glutamate (GPE), providing the first pharmacological treatment specifically for Rett syndrome [2]. As in previous clinical trials for NDDs, Daybue's LAVENDAR trial utilized caregiver and clinician impressions of patient symptoms as the primary outcome measures for evaluating treatment efficacy [2]. While feasible and implementable, subjective patient outcome measures lack quantitative sensitivity and are prone to placebo effects, partially contributing to the challenges in conducting clinical trials for RTT and other NDDs [3]. Thus, clinical NDD research increasingly necessitates reliable, objective, and quantitative outcome measures, or biomarkers, to serve as primary readout for therapeutic development and assessment.

Evoked event-related potentials (ERPs) are small voltage changes in the brain that occur in response to specific sensory, motor, or cognitive events measured by electroencephalogram (EEG), providing a noninvasive medium for evaluating sensory information processing deficits in mammals [4]. Alterations in key polarity peak features, including peak amplitude and latency, reflect changes in the strength and timing of event-related cognitive processes, respectively. Additionally, altered event-related features, like evoked power and phase-locking factor (PLF) or inter-trial phase coherence (ITPC), which quantify the strength and trial-to-trial reliability of individual high (alpha, beta, gamma) and low (theta, delta) EEG frequency oscillation phase, are indicative of impairments in neural circuit activity and communication [5]. Accumulating clinical and preclinical studies have identified altered ERPs, such as auditory-evoked event-related potentials (auditory ERP or AEP) [5–8] and visual-evoked event-related potentials (visual ERP or VEP) [8–10], in conjunction with RTT symptoms, suggesting evoked ERPs may serve as potential biomarkers for RTT. In patients with RTT, visual- and auditory-evoked ERPs demonstrate sensory information processing delays and deficits, as indicated by increased peak latencies [6], decreased peak amplitudes [7–9], and prolonged response recovery [9]. Analogous visual- and auditory-evoked ERP disruptions are observed in several RTT rodent models [5,9–13], as well as decreased evoked power and PLF [5,11,12]. Further, altered ERP features correspond with disorder onset and severity in both patients and rodent models of RTT [5,9]. Collectively, these findings support that evoked ERPs are highly congruent across rodent models and patients with RTT, providing consistent neurophysiological outcome measures for evaluating RTT phenotypes and severity.

Previous studies have demonstrated that altered ERP features can be alleviated using genetic strategies in mouse models of RTT. Restoring MeCP2 protein expression solely in somatostatin or parvalbumin-expressing inhibitory neurons mitigated altered ERP features and RTT phenotypic scores in hemizygous MeCP2-deficient male mice [11]. Moreover, transgenically increasing MeCP2-T158M protein expression reduced ERP deficits and RTT phenotypes in a knock-in mouse model

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carrying the common RTT-associated mutation, MeCP2 T158M [12]. Alternatively, deletion of NMDA receptor subunit 2A in MeCP2-deficient mice normalized parvalbumin cell hyperconnectivity and evoked activity, alongside reduced hindlimb clasping and improved visual acuity [10]. Together, these findings suggested that altered ERP features can be rescued and reflect improved RTT symptomology. However, whether ERP features were sensitive to therapeutic intervention remained unknown.

In this issue of *Neurotherapeutics*, Dong and colleagues aimed to assess whether neurophysiological features, such as auditory-evoked ERPs (AEPs), could respond to pharmacological treatment with a positive allosteric modulator (PAM) of muscarinic acetylcholine subtype 1 receptor (M_1), after previously demonstrating improved RTT phenotypes following M_1 activity potentiation in MeCP2-deficient mice [14]. The team administered acute treatments of the M_1 PAM, VU0486846 (VU846), across a dose range from 1 to 30 mg/kg to evaluate dose-dependent effects on AEPs in a female heterozygous knock-out model of RTT [15]. Consistent with previous studies, MeCP2-deficient mice demonstrated altered AEP features including decreased peak amplitudes, increased peak latency, reduced evoked power, and reduced ITPC (or PLF) compared to wildtype littermates. However, acute treatment with VU846 (3 mg/kg, intraperitoneal injection) 30 min prior to testing ameliorated altered AEP features in heterozygous female MeCP2-deficient mice, providing evidence of auditory-evoked ERPs as pharmacologically responsive neurophysiological features in a translatable model of RTT.

Notably, ERP abnormalities have been consistently reported across multiple NDDs, including patients with and animal models of CDKL5 deficiency disorder (CDD), MECP2 duplication syndrome (MDS), FOXG1 syndrome, and autism spectrum disorder (ASD) [16–22]. The findings of Dong and colleagues raise the possibility that altered ERP features observed in other NDDs may be responsive to pharmacological treatment as well, implying a future direction to validate pharmacological sensitivity of altered ERP features in the above NDDs.

To date, multiple studies across patient and animal models have pointed to evoked ERPs as reliable and objective biological outcome measures for Rett syndrome, developing alongside disorder progression and paralleling disorder severity. The demonstration that auditory-evoked ERPs are sensitive and responsive to dose-dependent pharmacological intervention in a translatable rodent model of RTT highlights the potential to lean on this measure as a biomarker for RTT and likely other NDDs. Utilization of auditory-evoked ERPs, thus, provides a promising avenue to expedite pharmacodynamic dosage testing and pharmaceutical development in both preclinical and clinical settings.

Author contributions

J.M. and Z.Z. conceived the outline. J.M. provided the initial draft and finalized it with edits from Z.Z.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Zhaolan Zhou reports financial support was provided by National Institutes of Health. Other authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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