**Title:** Novel Performance-Based EEG Study of Behavioral Flexibility in Individuals with Fragile-X Syndrome

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**Introduction:** Fragile X Syndrome (FXS) is a monogenic disorder caused by an unstable trinucleotide repeat expansion with the fragile X mental retardation 1 gene (FMR1). FXS is the leading genetic cause of inherited intellectual disability and autism spectrum disorder (ASD). Behavioral flexibility, or the ability to shift and maintain new behavioral responses based on changes in environment, is highly impaired in FXS. Clinically, behavioral rigidity may look like resistance to change in routines and increased anxiety in novel or unexpected situations. Parent-report measures and larger neuropsychological testing batteries document behavioral flexibility deficits in FXS. Still the component neural processes underlying these deficits remain unclear. With limited mechanistic understanding, treatment development and symptom relief is stalled. Thus, identifying potential translational biomarkers of behavioral flexibility deficits in FXS can enhance disease understanding and advance behavioral and pharmaceutical treatment development. EEG offers an effective, relatively non-invasive method to identify brain processes affecting behavioral rigidity in FXS.

**Method:** During continuous EEG recording using a 128-channel EGI cap, participants were instructed to select the box in the correct location (as indicated by a coin). Unexpected reversals in behavioral response preference (as indicated by a red 'X') occurred randomly following 3-5 consecutive correct responses. Participants attempted two blocks of both 2-box and 4-box conditions. Number of reversals and reaction times were recorded. Raw EEG data were filtered using 2 Hz high-pass, 80 Hz low-pass, and 60 Hz notch filters. Data were epoched from -500 to 800 ms with respect to the onset of feedback stimuli (coin or red X) and baseline corrected using data from the -200 to 0 ms epoch preceding feedback stimuli. We examined three ERP components, each occurring following feedback onset: N1, P3a, P3b from either Fz cluster of 8 centro-frontal electrodes (N1, P3a) or Pz cluster of 6 centro-parietal electrodes (P3b). ERPs were defined as the minimum or maximum amplitudes in a time window centered on the grand average peak amplitude +/- 50 ms. Amplitude and latency were calculated for each participant average at each peak. Separate mixed effects ANOVAs were calculated for amplitude and latency of each peak with the between subjects factors group (FXS, TDC) and within subjects factor feedback type (reversal, non-reversal) and condition (2-box, 4-box). Last, we examined latency and amplitude of ERPs in relation to key clinical measures to determine the extent to which our neurophysiological indices may be potential biomarkers in FXS.

**Results:** Overall, individuals with FXS performed as well as TDC based on the number of reversals participants achieved in each task. Negative feedback produced a greater amplitude ERP compared to positive feedback in both groups. N1, P3a amplitudes were greater for FXS than TDC, for both reversal and non-reversal feedback. P3b was of greater amplitude and occurred later in the FXS group relative to TDC group. Social avoidance and stereotypy as rated by parents on the Aberrant Behavior Checklist predicted P3b amplitude and latency during reversal trials.

**Discussion:** In the first study of its kind in individuals with FXS, we provide new insights in the neurophysiological basis of cognitive flexibility deficits in this patient population. Though individuals with FXS performed as well as controls during the simple deterministic task, we showed individuals with FXS are overly responsive to visual feedback stimuli. This is consistent with findings of cortical hyper-excitability previously identified in sensory and association cortices, suggesting cortical hyper-excitability also is present in the frontal-striatum-parietal circuitry critical for behavioral flexibility. Differences in the time course and power related to processing feedback stimuli provides new insights into potential mechanisms underlying difficulty adaptively changing behavior dependent on reinforcement contingencies in FXS. Importantly, these brain-based biomarkers were linked to parent-reported clinical features of behavioral inflexibility, suggesting potential targets for future therapeutic interventions and translation to preclinical models.
References:


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