2021 Gatlinburg Conference Poster Submission

Title: Evaluation of Psychological, Neurocognitive, and Neurophysiological Phenotypes in FMR1 Premutation Carriers

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Introduction: Cytosine-guanine-guanine (CGG) trinucleotide repeats in the 5' untranslated region of Fragile X mental retardation 1 (FMR1) gene over 200 results in a "full mutation" of Fragile X Syndrome (FXS), whereas 55-200 repeats results in a "premutation". FMR1 premutation carriers (PMC) are characterized by a range of psychiatric, neurocognitive, and physical conditions, though different than those features associated with full mutation FXS. CGG repeat length, Fragile X mental retardation protein (FMRP) levels, and degree of toxicity resulting from CGG repeat containing FMR1 mRNA, and environmental factors are thought to play a role in the heterogeneous presentation of PMC. Studies have reported non-linear relationships with CGG repeat length and psychiatric and medical symptoms (Seltzer et al., 2012). Still there remains no known study to date examining neurophysiological processes in PMC. Studies using EEG in FXS have provided critical insight into underlying neurophysiology and links between established pathology and phenotypic presentation (Wang, Ethridge, Erickson, 2017).

Method: Forty-one females (17-78 years) with 50-200 CGG repeats, or premutation carriers (PMC), and fifteen age- and-sex matched controls completed the study. Blood samples were obtained from all participant to confirm premutation status and obtain CGG expansion and methylation assay. In addition, all participants completed: 1) neurocognitive testing via the Test of Attentional Performance for Children (KiTAP), 2) self-report measures including Beck Depression Inventory, Second Edition (BDI-II), Anxiety Sensitivity Index (ASI), and Adult Sensory Profile (SP); 3) eye tracking using Tobii T120 of Farzan faces and social preference scenes as previously reported (Hong); 4) five-minute resting state EEG using EGI NetAmp400. We conducted separate univariate ANOVAs for each variable of interest for each task with the between subjects' factor group (PMC vs TDC). Age and IQ were evaluated as covariates, but neither substantively altered results and thus were not included in final analyses. Cluster analysis with k-means was completed in order to assess whether distinct neurocognitive and psychological profiles could be identified among homogenous subgroups of PMC, regardless of sex and repeat count.

Results: PMC and TDC did not differ on IQ, depression or anxiety symptoms, or social or sensory processing ($p's>.05$). Across frequency ranges, groups did not differ on relative power ($p's>.05$). Longer and greater trial-to-trial variability reaction time during a basic processing speed task ($F=4.16$, $p=.046$), increased errors during a distractor task ($F=3.95$, $p=.052$), increased errors ($F=4.54$, $p=.038$) during a flexibility task in PMC relative to TDC. Preliminary analysis showed a three cluster solution for neurocognitive and psychological data with maximum distance between the different clusters confirmed by F-tests ($F's>3.84$, $p's<.03$). Cluster 1 (n=10) is primarily defined by altered cognitive and social processing; Cluster 2 (n=10) is primarily defined by elevated psychiatric symptoms; and Cluster 3 (n=14) represents a relatively neurotypical group with no significant elevations across variables. Repeat count differed based on cluster membership ($F(2, 30)=9.90$, $p=.001$), with Cluster 2 having the highest repeat count compared to Cluster 1 ($t=2.49$, $p=.02$) and Cluster 3 (; $t=4.50$, $p<.0010$). By the time of the conference, analyses will be conducted to examine further differences among clusters and correlations among variables and with CGG repeats.

Discussion: Our comprehensive analysis of FMR1 premutation carriers reveals relatively intact psychological, social, and neurophysiological indices, though subtle alterations in processing speed, distractibility, and flexibility are notable. Initial cluster analysis of PMC indicates three possible subtypes: a cognitive-social phenotype, a psychiatric phenotype, and a neurotypical phenotype. This finding may account, in part, for similar performance to controls at the group level. Analyses prior to the conference will confirm whether unique subtypes show distinct neurophysiological subtypes from each other and from controls. Overall, our findings expand upon existing PMC studies by demonstrating relatively normal neurophysiological profile, despite findings in FXS full mutations, suggesting neural hyperexcitability may be distinct to FXS pathology and complete absence of FMRP. Further, our findings indicate PMC subtypes may provide important insights into manifestations of certain symptoms and provide potential treatment options.