**Title**: Network Mechanisms Underlying Core Behavioral Features in Fragile X Syndrome

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**Introduction**: Fragile X Syndrome (FXS) is characterized by intellectual disability, sensory hypersensitivities, executive dysfunction, and autistic characteristics [1,2]. Current treatments only target specific psychiatric features (e.g., anxiety and irritability) and not cognitive features, which are more pressing for patients and families, due in part to poor insight into underlying neural mechanisms. Recent work from our group using resting state electroencephalography (EEG) has linked abnormal functional connectivity (FC) and specific microstates (i.e., transient, quasi-stable spatial patterns of brain activity across the scalp) to cognitive disruptions and lower IQ making FC an ideal target for investigation [3,4]. The current study aims to evaluate the underlying functional network disruptions using EEG to examine FC in source space during resting state and during a cognitive flexibility task. We aim to identify mechanisms contributing to functional disruptions in frontoparietal and temporal networks, with the goal of generating more specific, targetable biomarkers of the neurophysiology supporting cognition.

**Method**: A preliminary microstate analysis was conducted on resting state EEG data from 70 adult individuals (N=36 FXS and 34 typically developed controls (TDC)) ages 16-45, using the +Microstate Toolbox (K-means clustering to define microstates. Both a 4-cluster solution (i.e., replicates canonical microstates) and a 6-cluster solution were generated to replicate Takarae et al., 2023. Peak alpha frequency was also calculated as a proxy for cognition. The final results will include microstate outcomes from 80 adults (N = 40 FXS, 40 TDC) ages 18-36 to avoid both aging and developmental effects on cognition. Relationships between microstates and clinical measures indexing cognition will be evaluated using FC summary scores that represent whole functional networks as mediators within our statistical models. This approach aims to elucidate how specific underlying network disruptions correspond to distinct clinical features of FXS.

**Results**: Preliminary results show elevated global variance explained (GEV), i.e., the amount of original EEG data explained by the microstate solution, across microstates differed significantly between groups for both the 4-microstate solution (F(2, 67)=12.76, p<.001, ES=.16) and the 6-microstate solution (F(1, 68)=7.46, p=.008, ES=.1). Individuals with FXS exhibited greater GEV (**4:** M = 61.2%, SD = 7.8%; **6:** M=64.4%, SD=7.1%) compared to TDC (**4:** M=56.1%, SD=8.4%; **6:** M=59.3%, SD=8.4%). Further, GEV was inversely correlated with frontal peak alpha frequency (r = -.28, p = .019), with higher GEV associated with lower PAF. Next steps will include the FC analysis and assessment of a cognitive task where we hypothesize that there will be disruptions in the salience network, a network related to stimulus detection and attention, which will predict network stasis and difficulties with cognitive flexibility. Further, we will address whether microstates can be used as a less computationally intensive way to capture FC dynamics in FXS.

**Discussion:** The GEV findings are in alignment with prior findings in FXS where GEV elevation suggests network stasis and may reflect disruptions to underlying functional networks which may be associated with distinct cognitive and behavioral features of FXS, as suggested by the correlation with PAF.

**References:** **[1]** Salcedo-Arellano, M. J., Dufour, B., McLennan, Y., Martinez-Cerdeno, V., & Hagerman, R. (2020). Fragile X syndrome and associated disorders: Clinical aspects and pathology. Neurobiol Dis, 136, 104740. <https://doi.org/10.1016/j.nbd.2020.104740>; **[2]** Hagerman, P. J., & Hagerman, R. (2021). Fragile X syndrome. *Curr Biol*, *31*(6), R273-R275. <https://doi.org/10.1016/j.cub.2021.01.043>; **[3]** Hall, S. S., Jiang, H., Reiss, A. L., & Greicius, M. D. (2013). Identifying large-scale brain networks in fragile X syndrome. *JAMA Psychiatry*, *70*(11), 1215-1223. <https://doi.org/10.1001/jamapsychiatry.2013.247>; **[4]** Takarae, Y., Zanesco, A., Erickson, C. A., & Pedapati, E. V. (2024). EEG Microstates as Markers for Cognitive Impairments in Fragile X Syndrome. *Brain topography*, *37*(3), 432–446. <https://doi.org/10.1007/s10548-023-01009-z>; **[]**

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