2020 Gatlinburg Conference Poster Submission

Title: Exploring Cognitive Flexibility Deficits Using Behavioral Tasks in Individuals with Fragile X Syndrome

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Introduction: Fragile X Syndrome (FXS), a genetic disorder caused by a CGG trinucleotide repeat expansion in the fragile X mental retardation 1 (FMR1) gene, is the leading inherited cause of autism spectrum disorder (ASD) and intellectual disability. Deficits in cognitive inflexibility are among the most frequent reasons for clinic visits due to the profound distress they cause for patients and their families (Bishop et al. 2007; Lewis et al. 2006; Weber et al. 2019). Clinically, cognitive inflexibility can present as adherence to patterns and resistance to novel situations. In order to better understand the nature of cognitive flexibility deficits in FXS, we administered a reversal learning task previously validated for use in ASD (Amodeo et al. 2012; D'Cruz et al. 2016; D'Cruz et al. 2013).

Method: Thirty participants with FXS and fifteen chronologically age-matched and sex-matched typically developing controls (TDC) were recruited to complete the reversal learning task. Participants were instructed to choose between identical stimuli (a cartoon animal) presented on a computer screen for the one that is in the correct location by pressing a button that corresponds to its location on screen. Visual feedback is immediately provided in the forms of coins (correct, continue with same behavioral response) and red X's (incorrect, reversal on next behavioral response required). The task consisted of an Acquisition and a Reversal phase. During the Acquisition phase, participants have up to 50 trials to reach the criterion of consecutively identifying the correct location in 8 out of 10 trials. When the criterion was met, the correct location changed without warning and the Reversal phase began with identical criterion. The reversal learning task consists of four subtasks: 2-choice deterministic, 4-choice deterministic, probabilistic training (no reversal), and probabilistic reversal. During the deterministic subtasks, participants received 100% corrective feedback. During probabilistic subtasks, participants received 80% correct feedback and 20% incorrect feedback when the correct location was chosen. For each task, we examined number of trials to reach criterion and number of errors made. Differences between sexes were examined as were relationships with clinical measures.

Results: Results shows that the FXS group required more trials to reach criterion overall in all of the subtasks except for the 4-choice deterministic subtask. When analyzing the Acquisition and Reversal phases separately, the FXS group only required more trials than TDC in the Reversal phase in the 2-choice deterministic subtask but required more trials in both Acquisition and Reversal phase for the 2-choice probability reversal subtask. For each participant, errors were categorized as perseverative or regressive errors. Perseverative errors occur when the participant continues to choose the initial correct location during the Reversal phase despite receiving negative feedback. Regressive errors occur when the participant chooses the new correct location during the Reversal phase but then reverts to the initial correct location in subsequent trials. During 2-choice deterministic, the FXS group committed a greater number of perseverative *and* regressive errors compared to TDC. However, during 2-choice probabilistic, the FXS group committed more perseverative, not regressive, errors compared to TDC. During 4-choice deterministic, FXS committed a similar number of errors as TDC. Both FXS males and females required more trials to reach criterion and made more errors than controls during deterministic subtasks. However, during probabilistic subtasks, only FXS males required more trials to reach criterion than their TDC counterparts during probabilistic training (no reversal). Yet, during the probabilistic reversal subtask, *both* FXS females and FXS males required significantly more trials than their TDC counterparts. Last, FXS patients who required a greater number of trials to reach criterion during probabilistic tasks demonstrated most severe restricted, repetitive behavior on parent-report measures.

Discussion: In the first study of its kind in individuals with FXS, we confirm and extend previous findings. Our results show that FXS individuals demonstrate an initial learning deficit in situations with uncertainty. Additionally, we document that individuals with FXS have both a difficulty *switching* to and *maintaining* new behaviors compared to healthy controls; however, these specific impairments arise in different contexts of uncertainty. Though both FXS males and females demonstrated more impaired cognitive flexibility than controls during the probabilistic tasks, an interesting sex-specific pattern emerged in patients. Females

with FXS took fewer trials to reach criterion compared to males with FXS during probabilistic training. However, FXS males and females demonstrated similar level of impairments during the probabilistic reversal subtask. This finding is consistent with well-documented literature showing FXS females typically have higher cognitive functioning than FXS males; however, it also suggests that there may be a threshold in cognitive flexibility in FXS females. Overall, our findings add important insights into inflexible and rigid behavior in FXS and thus may help the development of more tailored interventions. Further, identification of clinical correlates suggests this task may be an appropriate proxy of rigid behavior in FXS, implicating its potential use in future preclinical models and cross-species drug studies.

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