AN ASSAY TO STUDY SUSCEPTIBILITY TO DISTRACTORS IN A MOUSE MODEL OF FRAGILE X SYNDROME

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A capstone project submitted for graduation with University Honors

May 6, 2022

University Honors
University of California, Riverside

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ABSTRACT

Fragile X Syndrome (FXS), is the most common inherited form of mental impairment associated with sensory issues, learning disabilities, cognitive impairment, and deficits in social interaction. However, the mechanisms through which sensory abnormalities influence learning a goal-directed task is unknown. To address this, we designed a go/no-go task in a well-studied mouse model of FXS - *Fmr1* knockout (*Fmr1* KO) mice. Mice learned a visual discrimination task consisting of sinusoidal gratings drifting in two orthogonal orientations. $Fmr1^{-/-}$ mice exhibited delayed learning and susceptibility to distracting auditory and visual stimuli, indicating hypersensitivity and inability to tune out distractors. This assay provides a valuable tool to study sensory hypersensitivity in the context of FXS and identify the associated circuit impairments.

ACKNOWLEDGEMENTS

I would firstly like to express my deepest gratitude to my faculty mentor, Dr. Anubhuti Goel, for her tremendous support and unwavering guidance throughout the completion of this project, even under outstanding circumstances. She has played the most important role in my undergraduate career by building my foundational skills and love for behavioral neuroscience and allowed me to develop a profound appreciation for the field. This experience has changed my life going forward.

I would like to thank everyone at the Goel Lab for progressing me on my journey of developing research skills and immersing me in the process of conducting a complex and innovative scientific project. A special thanks to graduate student Noorhan Rahmatullah, for her positive mentorship at every step of the way and taking the time out of her day to educate and work with me. I also want to sincerely thank graduate student Courtney Scaramella, who has graciously contributed to the data collection of this project.

I would like to thank the Honors faculty staff, such as Dr. Richard Cardullo and honors counselor Mayra Jones in providing me the opportunity to conduct this project, and Dr. Aaron Seitz in connecting me to the lab that reinvigorated and aligned me with my passions.

Lastly, I would like to thank my parents, Anurag and Bhavna Shukla, my family, and my loving friends, who have provided me with constant encouragement and bolstered me forward everyday.

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INTRODUCTION

FXS is the most commonly identified cause of inherited intellectual disability and is also the most common known cause of autism or autism spectrum disorders (ASD) (Stone, 2022). ASD is an umbrella term that refers to a large range of developmental and neurological disorders characterized by intellectual, social, and behavioral disability (Lord et al., 2018). It describes a constellation of early-appearing social deficits and repetitive sensory-motor behaviors. FXS is caused by a triplet expansion that inhibits expression of the FMR1 gene, located on the X chromosome (Bagni et al, 2012). Estimates report that FXS affects approximately 1 in 2,500 to 5,000 men and 1 in 4,000 to 6,000 women (Bagni et al, 2012). Those affected can present severe behavioral alterations, such as hyperactivity, impulsivity, anxiety, sensory hypersensitivity, cognitive inflexibility, seizures, as well as social behavioral impairments (Razak et al., 2020). Limited evidence demonstrates that there are relative impairments linked to executive dysfunction, specifically with working memory (Razak et al., 2020). There is no empirical cure for FXS, but behavioral, cognitive, and other therapeutic interventions can improve experienced symptoms and deficits.

Atypical sensory processing is a core feature of the Fragile X phenotype and ASD (Thye et al., 2017). Individuals with ASD exhibit abnormal visual perception and impairments in estimating the duration of visual stimuli, discriminating between visual stimuli, and have difficulty processing and integrating sensory input (Robertson & Baron-Cohen, 2017). Sensory discrimination is critical to many brain functions and decision making, therefore deficits in sensory processing can contribute to subsequent impairment in social behavior and other autistic traits, such as learning and memory deficits (Marco et al., 2011). The Autism field recognizes that the negative impact can encompass virtually all activities of daily living, such as a trip to the

grocery store, activities in the classroom or a birthday party. A better understanding of perceptual learning issues in FXS in combination with a dissection of the circuit mechanisms will allow identification of potential therapeutic avenues for a range of autistic symptoms (Goel et al., 2018).

The well-characterized animal model of FXS – the *Fmr1*$^{-/-}$ mouse reflects and reproduces several aspects of the disorder in humans and has been the most widely studied animal model of FXS (Goel et al., 2018). The field has progressed considerably in terms of understanding symptomology and underlying genetics in humans with FXS and animal models, but there is not extensive literature on preclinical animal models of FXS that examine circuit mechanisms. This parallel "mouse/ human" perspective, derived from a circuit-level understanding of FXS symptoms, is a novel approach to targeting therapeutic interventions (Goel et al, 2018). *Fmr1*$^{-/-}$ mice not only manifest the immature synaptic defects seen in humans, but also multiple symptoms such as anxiety, impaired cognitive flexibility, reduced social interaction, hyperarousal, and sensory over-reactivity, that could result from altered sensation. The monogenic origin of the disorder and its significant overlap with autism makes FXS ideally suited to address atypical sensory processing in ASD (Razak et al., 2020). The point of these studies is to examine the developmental transience of phenotypic differences between gene knockout and wildtype (WT) mice. Although many psychiatrists and clinicians have reported hypersensitivity to sounds and lights in individuals with FXS, the neural underpinnings of hypersensitivity are known and fragile X mice are an ideal model system to design an assay for distractibility and examine the underlying neural correlates.

Currently, we lack a clear and detailed understanding of perceptual learning, visual, and auditory discrimination impairments and the altered behavioral responses to distractors that FXS

individuals manifest. Through examining both wildtype and *Fmr1*$^{-/-}$ mice in a behavioral task, we can better understand specifically their susceptibility to visual or auditory distractors and how it affects their performance on a decision-making task. We show that expert *Fmr1*$^{-/}$ mice exhibit a disruption in performance of a visual discrimination task in the presence of multimodal distractors in comparison to wild-type (WT) mice, indicative of enhanced susceptibility to distractors in FXS.

METHODS

Experimental Animals

All experiments occurred at the University of California, Riverside and followed US National Institutes of Health guidelines for animal research, under an animal use protocol (IACUC #A20190036) approved by the Institutional Animal Care and Use Committee and Office of Research Integrity at the University of California, Riverside. We used young male and female adult (2-4 months) FVB WT and *Fmr1*$^{-/-}$ mice. All mice were housed in a vivarium with a 12/12-h light/dark cycle and all experiments were performed during the light cycle. FVB *Fmr1-/-* mice were chosen because FVB mice exhibit clear dysfunction in sensory processing and better breeding patterns. We also used homozygous litters to ensure better survival rates, as pups with different genotypes might receive unequal attention and care from dams.

Surgical Procedure

Headbar attachment surgeries were performed at 6-8 weeks on the two different mouse lines mentioned above. First, mice were anesthetized with isoflurane (5% for induction, 1.5-2% for maintenance during surgery) using procedures approved by IACUC and then placed in a stereotaxic frame with a nose cone and ear bars to secure the head. Toe pinches were used to ensure the animals were fully sedated during the surgical procedure. Once the skull was exposed, a U-shaped aluminum bar was glued in the center and secured with dental cement in order to subsequently head-restrain the mouse during behavioral tasks. The mice then receive post-operative care to fully recover from the cranial window surgery and headbar attachment.

Handling & Habituation

Post-surgery, the mice undergo a handling phase, habituation phase, and a pre-training phase. In training to perform the visual discrimination task, a behavior protocol was followed to accustom them to their learning environment. Mice were handled for 5 minutes each day for a period of three days for both genotypes to acclimate the mice to the experimenter to prevent the mice from stressing out during handling. Sunflower seeds were used as a reward after the handling. By the end of the handling phase, mice have acclimatized to the experimenter, and are ready to move on to the habituation phase.

Upon starting habituation, water deprivation also begins. Mice were given a restricted supply of water once a day, 0.7-1.5 mL of water. For three days and 15 minutes per session, they were placed in the behavior rig for habituation to the soundproof chamber. They were head-restrained, placed on the 8cm polystyrene ball suspended in air, and allowed to run on it. On day 1 of the habituation session, mice were introduced to the head restraint and running on the ball. On day 2, mice were introduced to the sound of fans, the sound of the vacuum pump, the visual stimulus presented on the monitor, and the red-light fixture. On day 3, mice were introduced to the lickport that dispensed water. Initially it was placed at a distance of 5-6 mm from the snout. The water deprivation during habituation is employed to motivate mice to lick and seek reward once the pretrial phase begins. Once habituation has occurred and approximately 15-20% weight loss has occurred due to water deprivation, the pretrial phase begins.

Pretraining

After a level of established comfortability, the mice moved on to the pretraining tasks. The pretraining phase lasted between three and nine days depending on performance. During

pretrials the screen displays sinusoidal gratings drifting in eight different directions. The screen was presented at a distance of 35 cm from the mouse, and the visual stimuli will be randomly presented for 3 s at a time. Each stimulus was paired with a ~3 μL (0.003 mL) water reward administered through the lickport approximately 2 s after the stimulus was presented. The purpose of this task is for the mice to learn to make an association between the water reward and the presentation of the stimulus, while simultaneously learning that no water reward is presented during the inter-trial interval (ITI) of 3 s. Once the association is made, they must learn to lick with a minimum of 80-85% accuracy. They are then able to be administered the visual discrimination paradigm, also known as the go/no-go task.

Go/No-Go Visual Discrimination Task

In the go/no-go visual discrimination task, mice were trained to discriminate between two different visual stimuli presented on the monitor. The visual stimulus is a presentation of sinusoidal gratings that drift in two orthogonal directions at a temporal frequency of 2 Hz and spatial frequency of 0.01 cycles/degree and 100% contrast. The gratings were displayed for 3 s while a water reward is given 2 s after presentation of the stimulus. Drifting sinusoidal grating orientations at a 45° and 135° orientation were used from the given task, with 45° being the preferred stimulus and 135° being the non-preferred stimulus. Although the two different stimulus orientations are presented at random, the water reward was only paired with the 45° orientation, the preferred stimulus. Mice were trained to learn to discriminate between the two orientations and lick when the preferred stimulus at a 45° orientation is presented, which is referred to as ‘go’. They must withhold licking when the non-preferred stimulus at a 135° orientation is presented, referred to as ‘no-go’. Licking was recorded during the 3 s period of

stimulus presentation, as the lick onset time begins right when the stimulus is presented. However, only licks between 2 s and 3 s (water reward period) will be accounted for the behavioral response. The behavioral responses of the mice were categorized as a “Hit,”, “Miss,”, “Correct Rejection” (CR), or “False Alarm” (FA). Any incorrect response (Miss or FA) was followed by a time-out period for 6.5s, during which nothing was presented on the screen. Training sessions start with 250 trials and progress to a total of 350 trials. Time and sessions taken to complete the tasks varied based on accuracy during performance. Sessions can continue from three to eight days. Different contrasts were tested previously to obtain a psychometric threshold for optimal performance on the visual discrimination task (Goel et al., 2018). To statistically analyze performance on tasks, the d’ (discriminability index) was calculated using the following equation:

$$d' = norminv(Hits/Hits+Misses)-norminv(FAs/FAs+CRs)$$

Norminv is a function of Matlab that returns the inverse of the normal cumulative distribution function.

Mice must surpass a d’ of 1.5 to render them as expert mice. They can then move on to the second phase of the behavior task.

Note on Data Exclusion

During data collection, external factors can influence the animal’s performance and behavior that do not reflect the ability of mice to discriminate between the stimuli. These factors/variables include, poor health due to extreme weight loss and technical issues related to

the behavior set up. Three d' values from a WT in Figure 2c, that were influenced by these variables were excluded.

Go/No-go Visual Discrimination Task with Presence of Multimodal Sensory Distractors

The second phase of the behavior task entails the same preferred stimulus (drifting sinusoidal grating orientations at a 45° orientation) and non-preferred stimulus (drifting sinusoidal grating orientations at 135° orientation) will be presented at random. On 50% of the trials, distracting stimuli will be delivered as the target visual stimulus is presented for 3s. The distractors used are auditory and visual in nature. The auditory distractor sounds at a frequency of 5000 Hz, as the mouse hearing range is between 1000 and 91,000 Hz. The audible sound was played in the first 1.5 s of the 3 s visual stimulus presentation. There is one pulse for 1.5 s, and the loudness level was kept consistent. Without the auditory distractor, the sounds of the air from the ball setup, the vacuum pump, and the fans add up to a baseline of approximately 65 dB. When the auditory distractor is sounded, it increases to 95 dB. The visual distractor entails custom-made bright flashing LED lights bordering the screen of the monitor. This distractor was also presented simultaneously with the auditory distractor, accounting for the multimodality of sensory discrimination.

Licking was again recorded during the 3 s period of stimulus presentation, such that the lick onset time began right when the stimulus and distractors were presented. Only the licking between the 2s and 3 s water reward period was accounted into the behavioral response. The behavioral responses were also categorized as a "Hit," "Miss," "Correct Rejection" (CR), or "False Alarm" (FA). Any incorrect response (Miss or FA) will be followed by a time-out period for 6.5 s, during which nothing will be presented on the screen. Training sessions on the

distractor task comprised 200 trials each and sessions will be conducted until the mice surpass a d' of 1.5. The d' will be calculated using the same aforementioned equation.

After the mice have gained proficiency in performing the visual discrimination task in the presence of auditory and visual distractors with a d'>1.5, they must complete the original go/no-go task without distractors to establish that they have not forgotten the task. Lastly, they perform a control task for the purpose of seeing if they actually learned the task. For the control task, the screen displaying the visual stimulus was turned off with no distractors presented. Good performance on this task (a high d'), indicates that the mice are indeed licking based on the visual stimulus and not cheating by sensing the water delivery with their whiskers.

Visual stimuli and auditory distractors will be presented using custom-written programs as well as Psychtoolbox in MATLAB. These will also be used to dispense water from the lickport and acquire data.

RESULTS

Fmr1$^{-/-}$ mice are able to complete the pretraining task at the same level as WT controls

To investigate perceptual learning deficits linked with abnormal visual sensory discrimination in FXS, male and female *Fmr1*$^{-/-}$ mice (n=1) and wild-type (WT) (n=5) mice were trained on a go/no-go visual discrimination task. Prior to learning this go/no-go visual discrimination task, they underwent a pretraining period (see Methods). During the pretraining period, head-restrained young adult mice (2-4 months old)

were placed on an air-suspended polystyrene ball and presented with sinusoidal gratings drifting in eight different directions on a monitor screen. The visual stimuli were randomly chosen from a set of 8 orientations. Each visual stimulus was presented for 3 s; and 2s after the stimulus onset a water reward was delivered (Fig 1b).

Figure 1: Pre-training Task

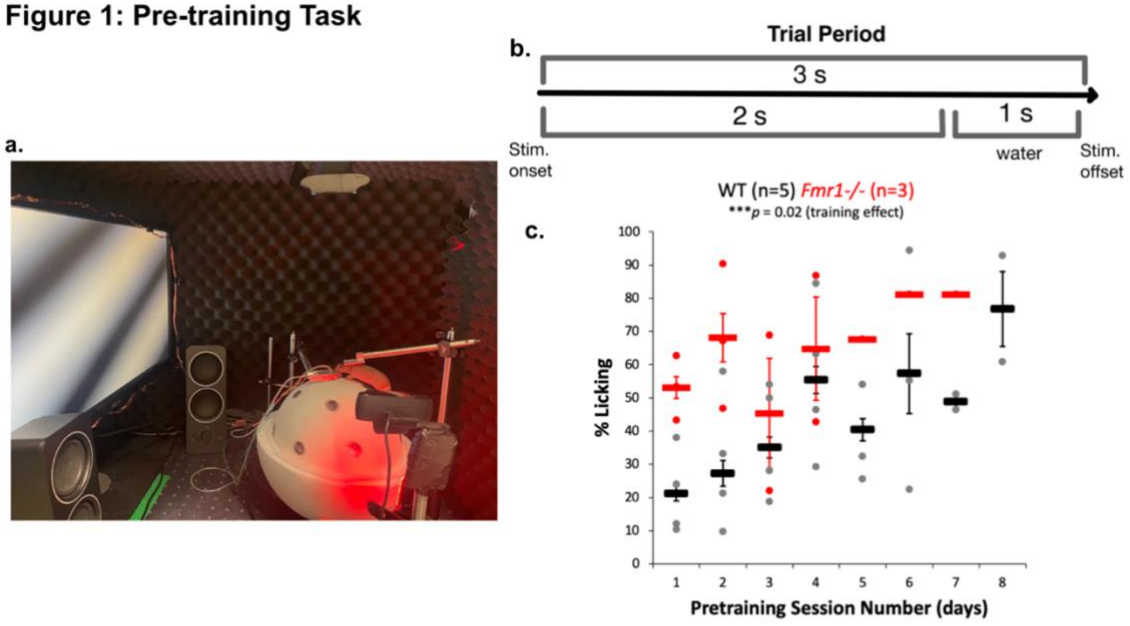

Figure 1. a. Image of the behavioral rig; b. Visual schematic of the timeline of an individual trial for the pretraining task and during which interval the water reward is dispensed; c. Scatterplot comparing amount of sessions taken to reach the desired 'percent licking' by WT controls and *Fmr1*$^{-/-}$ mice, establishing learning of association between visual stimulus and reward (* p = 0.02, effect of training) (Red dots indicate *Fmr1*$^{-/-}$ mice data points)

The pretraining phase allows mice to learn to associate the presented visual stimulus with a water reward and that the water reward is only presented during the end of the stimulus presentation. The stimulus was followed by an inter-trial interval (ITI) of 3s, with no punishment. Performance during the pretraining period was quantified by 'percent licking', to calculate the proportion of trials during which the mice licked and therefore exhibited a "hit" response. Each daily session consisted of 250 trials, and mice were only advanced to the go/no-go task upon achieving a licking percentage of 80-85% . Our data shows that there was an overall effect of training for this session type for the WT controls (ANOVA, *p=0.0217, n=5 for WT mice). There was also a significant difference, which is strongly indicative of learning occurring during the process and an association being made with visual stimuli to water reward. Figure 1c demonstrates that there are no differences in performance of *Fmr1*$^{-/-}$ mice (n=1) on the pretraining task. WT mice take on average, 6.2 ± 1.78 days to reach above 80% licking, while *Fmr1*$^{-/-}$ mice also take on average 7 days to meet the accuracy minimum.

Fmr1$^{-/-}$ mice demonstrate delayed learning on a visual discrimination task

After the pretraining period, both WT and *Fmr1*$^{-/-}$ mice were trained to perform a go/no-go task that requires perceptual visual discrimination. Mice were now presented with sinusoidal gratings drifting in only two orthogonal directions, with 45° being the preferred, 'go' response and 135° being the non-preferred, 'no-go' response. An incorrect behavioral response elicited a 6.5s 'time-out' period. Task performance was quantified using the discriminability index statistic d' (see *Methods*). The mice were not administered the next level of task until gaining expertise in the go/no-go task. Mice were rendered experts after achieving a d'>1.5. In line with our previous study, it is again demonstrated that *Fmr1*$^{-/-}$ mice experience a significant delay in achieving a d'

greater than 1.5 compared to WT controls. WT mice learned quickly, on average 4 days, to lick in response to the preferred orientation and to withhold licking upon the non-preferred orientation. *Fmr1*$^{-/-}$ take on average 8 days to achieve the desired d'. However, *Fmr1*$^{-/-}$ eventually reach equivalent expert d' levels as WT mice (days to reach d': 4 ± 2.16 days vs 8.3 ± 4.04 days for WT and *Fmr1*$^{-/-}$ mice, respectively) (Fig 2c).

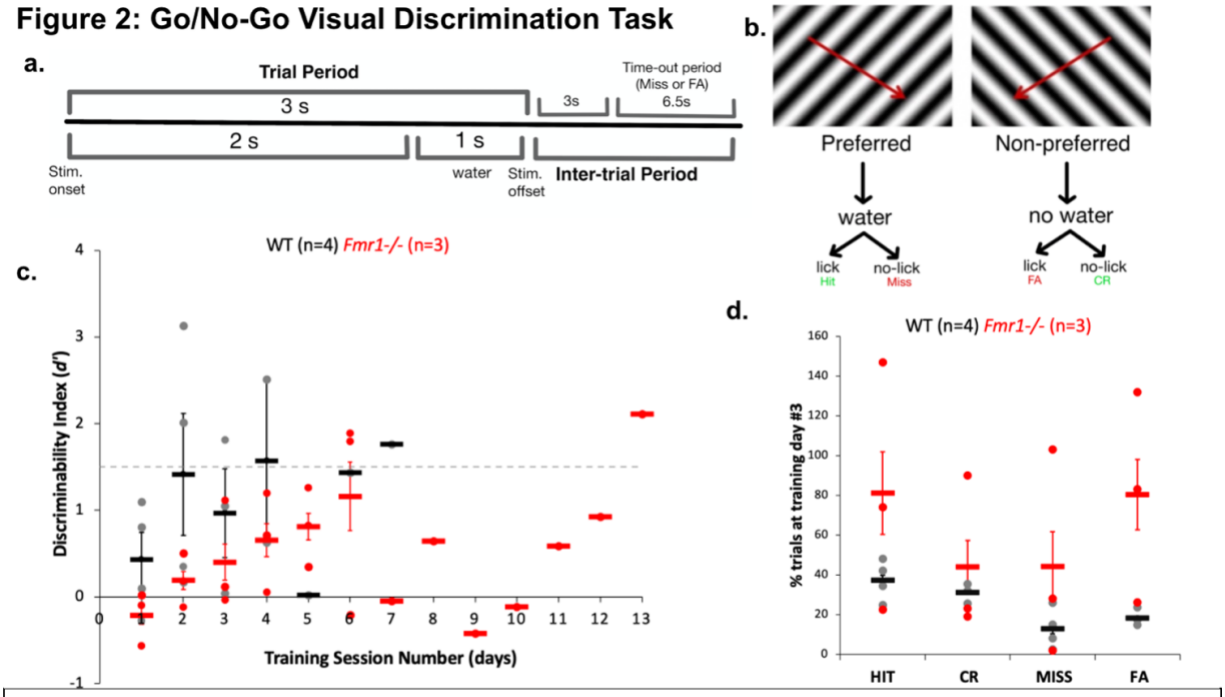

Figure 2. a. Visual schematic of the trial period, water reward presentation, and time-out period for the Visual Discrimination Task; b. Visual Schematic of the preferred vs. non-preferred visual stimulus presented on the monitor, with their associated responses; c. Scatterplot comparing the number of sessions taken to achieve the desired d' of 1.5 by WT controls and *Fmr1*$^{-/-}$ mice; d. Scatterplot of amount of trials in which mice gave the preferred responses ('Hit', 'CR') and non-preferred responses ('Miss', 'FA') on session day 3 (Red dots indicate *Fmr1*$^{-/-}$ mice data points)

A comparison between session 1 and session 4 of WT mice showed a significant increase in d' (paired test, p=0.03, n=3 for WT mice). Behavioral responses were further analyzed over the course of training, with a visible upward trajectory in 'Hit' and 'correct rejection' (CR) responses, and an apparent decrease in 'Miss' and 'false alarm' (FA) responses, as both genotypes learned the task (Fig 2d). *Fmr1*$^{-/-}$ mice exhibited a significantly higher percentage of

'Miss' and 'FA' responses, and a significantly lower percentage of 'Hit' and 'CR' responses in comparison to WT mice at session 3 (Fig 2d). Session 3 was chosen for analysis, as on average, at this stage in the task, WT controls are already demonstrating high rates of the preferred response, with diminishing rates of the non-preferred response. This discrepancy in the *Fmr1*$^{-/-}$ mice responses likely contributed to their poor performance during early training sessions and explains the longevity of their go/no-go visual discrimination task training period. Both WT and *Fmr1*$^{-/-}$ mice exhibited significant improvements in task performance throughout training. Even though *Fmr1*$^{-/-}$ mice took, on average, twice as long to achieve a d'>1.5, there was no significant difference in the final d' values between the two genotypes. Therefore, *Fmr1*$^{-/-}$ mice eventually reach the same level of performance in this visual discrimination task as WT controls but show a delay in the period of time taken to achieve it.

Multimodal Sensory distractors worsen the performance of *Fmr1*$^{-/-}$ mice on a visual discrimination task

Apart from attributing performance contrast to differing sensory processing and cognitive ability, it was considered that distractibility, inattention, or impulsivity contributed significantly to the delay in perceptual learning of *Fmr1*$^{-/-}$ mice. For this reason, after reaching expert status on the visual discrimination task, mice were introduced to the multimodal distractor task. The distractor task is an adaptation of the go/no-go task, modified only to incorporate spontaneous sensory distractors during the task. This encompassed trials with both auditory distractors consisting of loud tones (one pulse lasting 1.5s at 5000 Hz), and a visual distractor (custom-made bright flashing LED lights bordering the monitor screen). Sensory distractors were delivered at random in 50% of the trials, simultaneous with the onset of the visual stimulus. WT mice again learned

quickly, with an average duration of 3 days to reach the desired d'. *Fmr1*$^{-/-}$ mice take on average 4 days to achieve the desired d' (days to reach d': 3 ± 1.5275 days vs 4 days for n=3 WT mice and n=1 *Fmr1*$^{-/-}$ mice, respectively) (Fig 3d). WT mice continued to exhibit good performance and an upward trend in daily sessions. This demonstrated to us that the effects of distractors on task performance maintains the previously established trend of delayed learning.

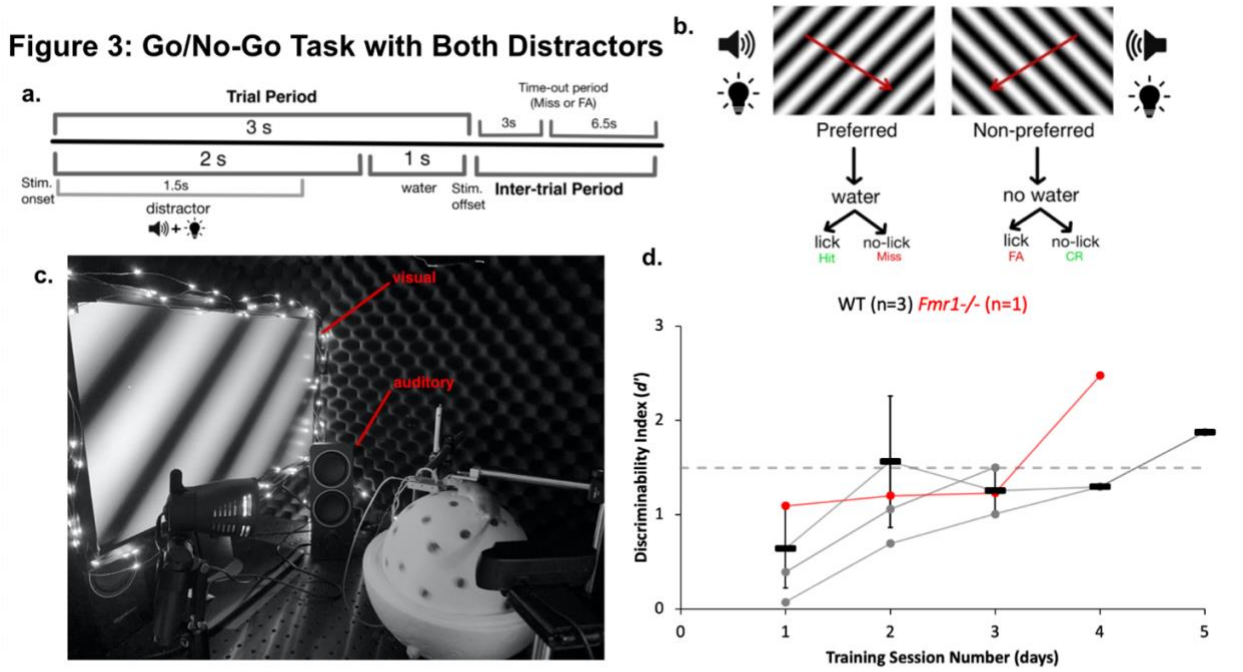

Figure 3. a. Visual schematic of the timeline of one individual trial of the visual discrimination task with BOTH sensory distractors; b. Visual schematic of the preferred vs. non-preferred visual stimulus presented on the monitor, with their associated responses; c. Picture highlighting how the auditory and visual distractor are delivered in the behavioral rig; d. Scatterplot with lines comparing the number of sessions taken to achieve the desired d' of 1.5 by WT controls and *Fmr1*$^{-/-}$ mice on the visual discrimination task with BOTH distractors

To facilitate a better understanding of each distractor's individual role in both genotype's performance, a session of solely the auditory distractor, and a session of solely the visual distractor was added after reaching expertise with both distractors (achieving a d'>1.5). Since the sensory distractors were delivered at random in 50% of the trials, d' was calculated separately for trials with distractor and without. There was no change in the performance of WT mice with

auditory or visual distractor alone compared to their score on the go/no-go task without any distractors, also referred to as the last 'learned session' (Fig 4c & Fig 4d). On the distractor task with only the auditory distractor, average WT performance (d') differed by only 0.224, while average *Fmr1*$^{-/-}$ mice performance differed by 2.59, much more pronounced (Fig 4c). On the distractor task with only the visual distractor, average WT performance differed by only 0.4929, while average *Fmr1*$^{-/-}$ mice performance differed by 2.7127, again, far more distinct (Fig 4d). This is largely indicative of the fact that WT mice are able to overcome the presence of the sole distractor quickly and maintain good performance on the task, while *Fmr1*$^{-/-}$ mice performance is severely impaired when attempting to do the learned task accompanied by distractors.

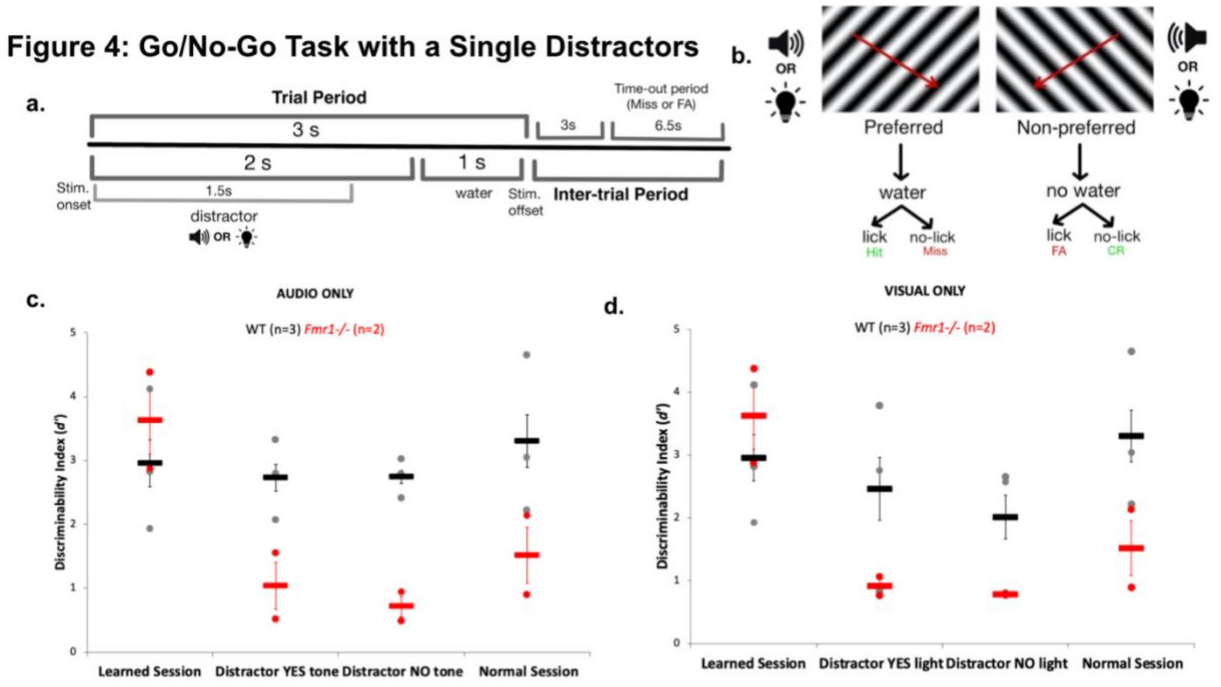

Figure 4. a. Visual schematic of the timeline of one individual trial of the visual discrimination task with EITHER sensory distractor; b. Visual schematic of the preferred vs. non-preferred visual stimulus presented on the monitor with either distractor, with their associated responses; d. Visual representation comparing the d' of both WT controls and *Fmr1*$^{-/-}$ mice on the last performed visual discrimination task without distractors ('Learned Session') to trials of the distractor task with and without the chosen distractor present, to a normal session of the visual discrimination task performed after ('Normal Session') (Red dots indicate *Fmr1*$^{-/-}$ mice data points)

Finally, both genotypes of mice had to perform both an extra visual discrimination task and a control task following completion of the variety of distractor tasks, referred to as the 'normal session' (Fig 4c & 4d). This extra task was implemented in order to ensure that the original visual discrimination task, the go/no-go task, was not forgotten and indeed learned throughout the experimental process. Both genotypes either maintained or improved their performance on this task from the previous time completed, suggesting that learning had occurred and did not diminish (Fig 4c & 4d).

Lastly, they completed a control task which was the original visual discrimination task, however, with the monitor off. A high d' on this task would reveal that the mouse was likely cheating and was unaffected by the visual stimulus in their performance. Both WT and *Fmr1*$^{-/-}$ genotypes received d'$\lesssim$0.

DISCUSSION

If an individual with Fragile X Syndrome (FXS) perceives normal stimuli as overwhelming, or is unable to tune out irrelevant stimuli then, he/she could limit social interactions (avoiding eye contact or hugging) and experience delays in learning and adapting to changes in the environment. Therefore there is no doubt that we need to examine sensory issues in FXS in order to solve higher order cognitive issues. Currently, there exists neither a cure for FXS nor any therapy that can reverse its core pathogenic mechanisms. Recent clinical trials to test the efficacy of mGluR antagonists, minocycline and arbaclofen, have been alarmingly unsuccessful (Mullard, 2015). One big challenge for drug development in neurodevelopmental disorders is the need to identify more reproducible phenotypes in animal models that reflect human symptoms and can be measured quantitatively with parallel assays (Erickson et al., 2018). Previously existing tasks employed as a measure to study rodent behavior do not maintain the same translational potential

of human experimentation, such as the marble burying task (MBT). The MBT is commonly used as an assay to study repetitive and compulsive-like behaviors in mice, however it lacks the construct and predictive validity for the human disorders they are modeling. Given that marble-burying is most closely related to the natural behavior of an animal, the behavioral aspects are not relevant when replicating in a human model and has no translational value. We have designed a valuable tool–a novel distractor task where *Fmr1* KO mice learn to discriminate between two visual stimuli and their performance is then evaluated on the discrimination task in the presence of auditory and visual distractors. This is a simple yet very innovative task that captures the hypersensitivity issues experienced by humans with FXS. Indeed, through a collaboration with Craig Erickson's lab at Cincinnati, my mentor, Dr. Goel has implemented an analogous distractor task in humans with FXS and found deficits similar to mice (data not shown). Additionally, this very simple task, can be combined with cutting edge two photon calcium imaging techniques to examine the deficits in excitatory-inhibitory dynamics that contribute to hypersensitivity. Our data shows a strong indication of enhanced susceptibility to distractors and hypersensitivity in FXS, as *Fmr1*$^{-/-}$ mice are exhibiting a disruption and impairment in performance and learning when presented with a visual discrimination task, especially when accompanied by sensory distractors. While WT mice are able to overcome the presence of the distractors in a shorter period of time and are not as susceptible to visual or auditory disturbances, *Fmr1*$^{-/-}$ mice struggle to maintain the same level of performance and ability to learn at the same rate.

Using this well-established mouse model of neurodevelopmental disorder we have implemented a series of goal-oriented tasks, and thus our research is furthering the empirical understanding of perceptual deficits in FXS and susceptibility to distraction.

Most research around FXS and Autism has focused on the social, communication and cognitive difficulties associated with the condition. However, the recent revision of the diagnostic criteria for autism has brought another key domain of autistic experience into focus: sensory processing (Robertson & Baron-Cohen, 2017). Atypical sensory experience is estimated to occur in as many as 90% of autistic individuals and to affect every sensory modality: taste, touch, audition, smell, and vision (Tavassoli et al., 2018). Due to the hyperarousal experienced, hypersensitivity, tactile defensiveness, or gaze aversion is utilized by those affected (Baranek, 1997). Hyporesponsiveness to social and nonsocial stimuli predicts lower levels of joint attention and language in children with autism. Attention disengagement and behavioral processes may have relevance for identifying early risk factors of autism and for facilitating learning across contexts to support development, starting from childhood (Baranek, 2013).

An ambulance passing by with loud sounds and flashing lights can make the experience for someone with hypersensitivity debilitating. Although many clinicians and psychiatrists report sensory issues resulting in hypersensitivity, whether FXS mice also exhibit similar deficits is not known. By increasing competency of how distracting sensory information can impede one's ability to perform well on cognitive tasks, we are revealing crucial information that will allow the development of new treatments to hindered learning abilities as seen in FXS. Our rodent behavioral assay is a valuable tool that captures the susceptibility to multimodal distractors that are often experienced by individuals with FXS and can be easily adaptable to humans, this adding to the translational potential of this project.

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