AWARD NUMBER: W81XWH-19-1-0521

TITLE: **Developmental Acoustic Exposure as a Novel Approach to Treat Fragile X Syndrome**

PRINCIPAL INVESTIGATOR: **Khaleel A. Razak**

CONTRACTING ORGANIZATION: Regents, University of California, Riverside, CA

REPORT DATE: **August 2021**

TYPE OF REPORT: **Annual**

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland, 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
August 2021	Annual Report	01Aug2020-31Jul2021

4. TITLE AND SUBTITLE

Developmental Acoustic Exposure as a Novel Approach to Treat Fragile X Syndrome

5a. CONTRACT NUMBER
W81XWH-19-1-0521

5b. GRANT NUMBER
PR180819

5c. PROGRAM ELEMENT NUMBER

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Regents, University of California, Office of Sponsored Research, 200 University Building, University of California, Riverside, CA 92521-0217

8. PERFORMING ORGANIZATION REPORT

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

11. SPONSOR/MONITOR'S NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT: **The main goal of the proposed studies was to test the hypothesis that a combination of sound exposure and minocycline treatment provided to the mouse model of Fragile X Syndrome (FXS), will cause a long lasting benefit in terms of sensory hypersensitivity and behaviors as adults. This project addresses a major gap in the autism literature on when the appropriate treatment window is. The first year of the project period has been highly productive, despite the loss of a significant amount of time and resources to the pandemic-related shut-downs of our university. We have published five papers and two reviews in 2020 from this project. In Kulinich et al (2020), we showed the beneficial effects of early life 5Hz repetition rate sound exposure on hyperexcitability correlates in Fmr1 KO mice. This is one of the major aims of the project. In Lovelace et al (2020), we showed that minocycline treatment in adult mice has an impact on sound evoked EEG responses, but not resting EEG compared to vehicle treatment. In Pirbhoy et al (2020), we showed that a more specific inhibitor (SB-3CT) that works like minocycline to reduce matrix metalloprotease-9 (MMP9) given to developing mice (~P22) works to reduce EEG phenotypes, reverses inhibitory cell phenotypes and improves behaviors even with an acute injection. In Jonak et al (2020), we used a state-of-the-art 30 channel multielectrode array (MEA) system to record EEGs from mouse skull and showed regional differences in EEG phenotypes in adults. In Ngueyn et al (2020), we showed that auditory hypersensitivity correlates are found in the P21-P34 window. These papers provide the foundation for the current grant in testing the same phenotypes following sound exposure and minocycline. We have also analyzed pilot data in the reporting year to show that in the adults, peripheral cochlear function is not different between WT and KO mice. These indicate central auditory processing changes underlie abnormalities. We have now shown separately that sound exposure or MMP9 inhibition reduces phenotypes when given during development. In the next project year, we will test the combination approach and identify longevity of development vs. adult treatments.**

15. SUBJECT TERMS
Fragile X Syndrome, Sound Exposure, Development, Cortical Hyperexcitability

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	18	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. INTRODUCTION:

The proposed studies will test the hypothesis that a combination of sound exposure and minocycline treatment during early development will have long-lasting beneficial effects on symptoms of sensory hypersensitivity in a pre-clinical mouse model of Fragile X Syndrome (FXS), a leading known genetic cause of autism. These studies will identify for the first time the long-term efficacy of treatment during specific developmental windows in FXS. These data will have broad implications in the design of clinical trials for neurodevelopmental disorders by specifying optimal developmental treatment windows. The specific impact will be on the following areas of encouragement as identified in the call for proposals:

i. Identification and testing of novel therapies
ii. Research to establish early treatment
iii. Research to understand pathophysiology of FXS.

2. KEYWORDS: *Provide a brief list of keywords (limit to 20 words).*

Fragile X Syndrome, Sound Exposure, Development, Cortical Hyperexcitability

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The 3 major aims of the project are:

1. To identify optimal repetition rates of sound exposure to alleviate phenotypes of auditory hypersensitivity.
2. To test the hypothesis that combined sound exposure and minocycline treatment from P5 to P21 will reverse phenotypes of hyperexcitability in *Fmr1* KO mice.
3. To test the long-term impact of the combination treatment on auditory hypersensitivity.

What was accomplished under these goals?

Major activities

During the reporting year:

1. We have analyzed PV protein level with western blotting in auditory cortex (AC) of P21 male mice raised in a regular vivarium which we term as 'normal exposure' (NE) (WT, n=4, Fmr1 KO, n=4), mice that were raised in a sound attenuated chamber and unexposed to external sounds, which we term 'attenuated exposure (AE)(WT, n=4, Fmr1 KO, n=4), and mice that were sound exposed (SE) during the developmental period to 14 kHz sounds with a repetition rate 5 Hz (5 Hz WT, n=4; 5 Hz Fmr1 KO, n=4) or 1 Hz (1 Hz WT, n=4; 1 Hz Fmr1 KO, n=4). We found that PV protein level significantly increased in AC of both WT and Fmr1 KO mice exposed to 14 kHz sounds with a 5 Hz repetition rate, but not 1 Hz (Fig. 1). This supports our hypothesis that the specific sound parameters used are important in

activating specific cortical mechanisms, and the beneficial effects are not due to non-specific effects of sensory environment.

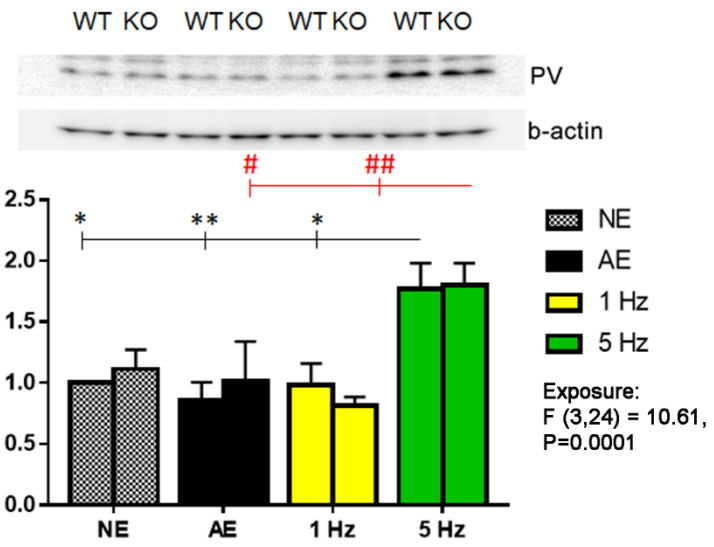

Fig. 1. PV protein levels increase in auditory cortex of both WT and KO P21 male mice after exposure to 14 kHz sounds with 5 Hz, but not 1 Hz repetition rate.
PV protein levels were normalized to β-actin in P21 auditory cortex of WT and *Fmr1* KO mice in NE, AE, 1 Hz SE and 5 Hz SE groups. In P21 auditory cortex of WT and *Fmr1* KO exposed to 14 kHz sounds with 5 Hz repetition rate (5 Hz), there was an increase in PV level compared to NE, AE and 1 Hz SE mice. Statistical analysis was done using two-way ANOVA with Bonferroni's post-hoc test (AE WT n=4; AE *Fmr1* KO n=4; 5 Hz WT n=4; 5 Hz *Fmr1* KO n=4; 1 Hz WT n=4; 1 Hz *Fmr1* KO n=4); * depicts sound exposure effect in WT mice, # shows sound exposure effect in *Fmr1* KO mice; */# $p < 0.05$; **/##, $p < 0.01$). There were no genotype differences.

2. We have also analyzed PV, PNN and cFos immunoreactivity with immunohistochemistry in AC of P21 male WT and *Fmr1* KO mice in NE, AE, 1 Hz SE and 5 Hz SE groups. We confirmed that similar to mice on FVB background (Kulinich et al., 2020), there was a decrease in the density of PV-positive cells in layers (L)4 and L5-6 AC of AE *Fmr1* KO mice compared to their WT counterparts on C57bl6 background (Fig. 2A). While PV cell density was increased in L4 AC of KO mice exposed to both 5Hz and 1 Hz repetition rate sounds, increase in PV intensity was observed only in AC of mice exposed to 5 Hz, but not 1 Hz (Fig. 2A-D), which corroborated western blot analysis results (fig. 1).

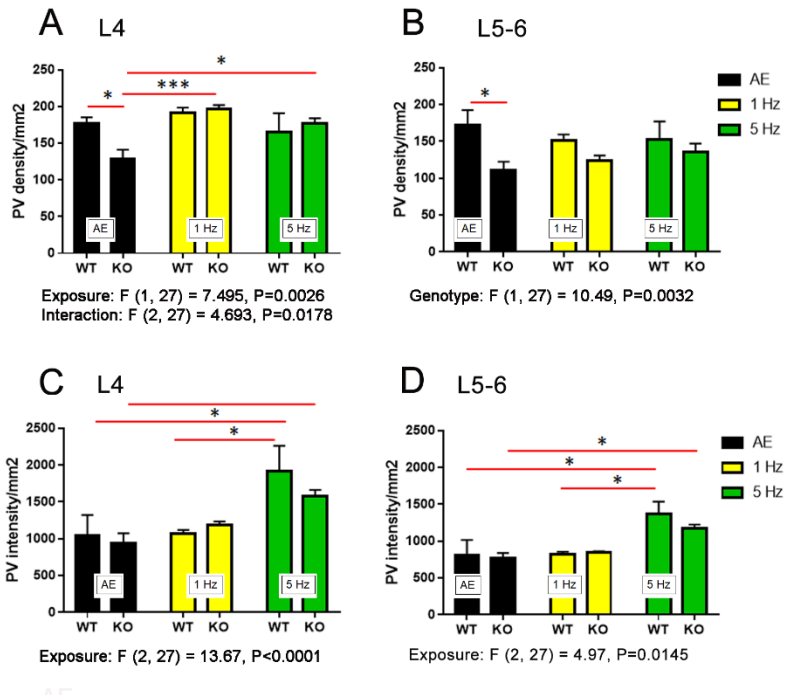

Fig. 2. Increase in PV intensity was observed only in AC of mice exposed to 14 kHz sounds with 5 Hz, but not 1 Hz repetition rate.
Analysis of PV cell density and intensity in L4 and L5-6 auditory cortex (AC) of WT and *Fmr1* KO mice in AE, 1 Hz SE and 5 Hz SE groups. Statistical analysis was done using two-way ANOVA with Bonferroni's post-hoc test (AE WT n=5; AE *Fmr1* KO n=6; 5 Hz WT n=7; 5 Hz *Fmr1* KO n=5; 1 Hz WT n=3; 1 Hz *Fmr1* KO n=7; *$p < 0.05$; *** $p < 0.001$).

3. There was a decrease in overall cFos cell density in L4 and L5-6 AC of Fmr1 KO mice exposed to 14 kHz sounds with 5 Hz repetition rate, but not 1 Hz (Fig. 3). Yet again, the influence of sound repetition

rates on outcomes suggests specific cortical mechanisms being activated. Importantly the sound exposure during development results in less number of cells being excited (as measured with cFos).

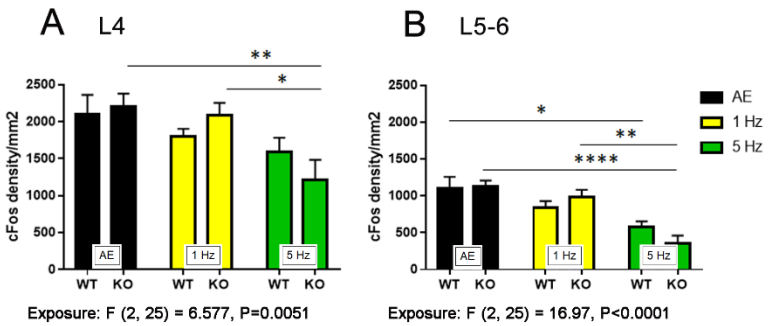

Fig. 3. Decrease in overall cFos cell density was observed in AC of KO mice exposed to 14 kHz sounds with 5Hz but not 1 Hz repetition rate. Analysis of cFos+ cell density in L4 (A) and L5-6 (B) auditory cortex of WT and *Fmr1* KO mice in AE, 1 Hz SE and 5 Hz SE groups. Statistical analysis was done using two-way ANOVA with Bonferroni's post-hoc test (n=5-7 mice; *p < 0.05; **p < 0.01 **** p < 0.0001).

4. There was no difference in density of PNN-positive cells observed in L4 and L5-6 auditory cortex of AE WT and AE KO and mice exposed to sounds with 5 Hz and 1 Hz repetition rate (Fig. 4A-C). Interestingly, there was a decrease in PNN cell intensity in AC of KO exposed to sounds with both 5 Hz and 1 Hz repetition rate (Fig. 4D).

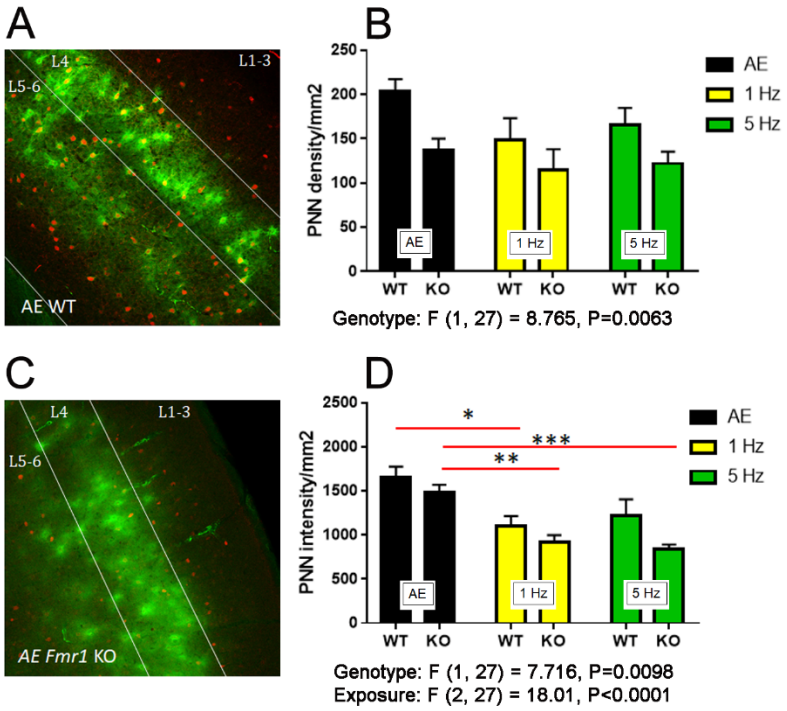

Fig. 4. Decrease in PNN intensity was observed in AC of KO mice exposed to 14 kHz sounds with both 5 Hz and 1 Hz repetition rate
Representative images of PNN positive cells (green) and PV (red) in AC of AE WT (A) and AE KO (C) and analysis of PNN cell density (B) and intensity (D) in L4 auditory cortex of WT and *Fmr1* KO mice in AE, 1 Hz SE and 5 Hz SE groups. Statistical analysis was done using two-way ANOVA with Bonferroni's post-hoc test (n=5-7 mice; *p < 0.05; ** p < 0.01, **** p < 0.0001).

5. To further investigate the effect of sounds with different repetition rates we have started EEG recordings in mice raised in AE and SE environments. We have already published the data for NE mice (Lovelace et al., 2018; Jonak et al., 2020; Pirbhoy et al., 2020) An EEG 2-channel electrode implant surgery was performed at P21 and after the 4-5 days recovery period (P25-P26) EEG recordings were performed. At the moment, we have recorded EEG from 21 male littermates raised in sound attenuation box (AE WT, n=6, AE *Fmr1* KO, n=15). Similar to NE mice (Lovelace et al., 2018), we found a significant decrease in synchronization to chirp-modulated sound at gamma range (30-100Hz) in FC of AE KO mice and a trend in AC with a plan to add 4 more WT mice to the analysis this month (Fig. 5). Next, we will be analyzing mice raised under the 5 Hz repetition rate sound exposure (SE), and will complete this experiment in the next progress report year and submit for publication.

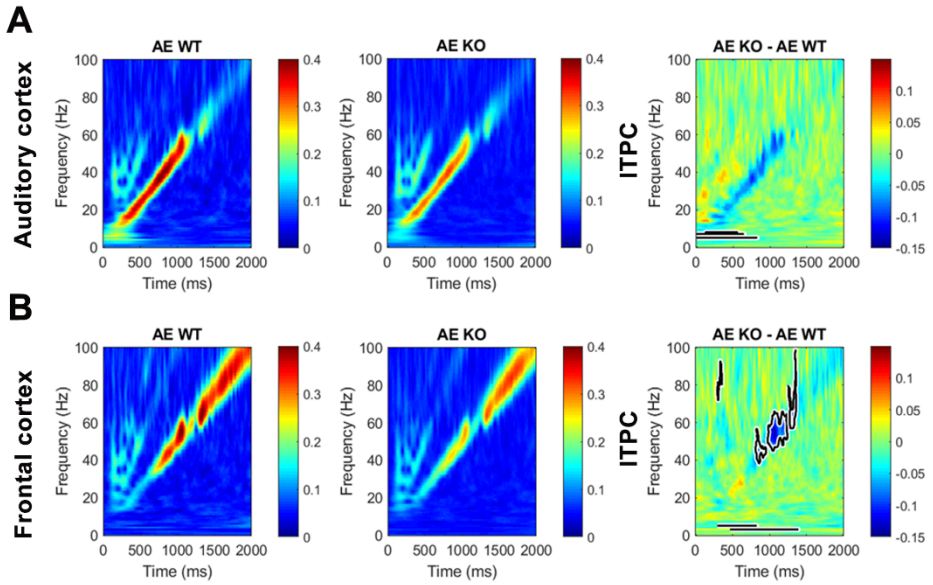

Fig. 5. Synchronization to chirp is impaired in frontal cortex (FC) of AE KO compared to AE WT mice
(A-B) Grand average matrices were calculated for each genotype (AE WT, left and AE KO, middle panels), and then average ITPC AE WT (n=6) value was subtracted from AE KO (n=15) value (right panels) for AC (A) and FC (B) Statistical cluster analysis reveals time x frequency bands that are significantly different between groups highlighted with bolded black borders.

6. We also found a significant increase in background non-phase locked single trial power (STP) during the chirp presentation in AC of AE KO compared to AE WT and a trend in FC with a plan to add 4 more WT mice to the analysis this month (Fig. 6), and complete the SE mice recording in the next reporting period. This is similar to our observations in the NE mice (Lovelace et al., 2020l Wen et al., 2019).

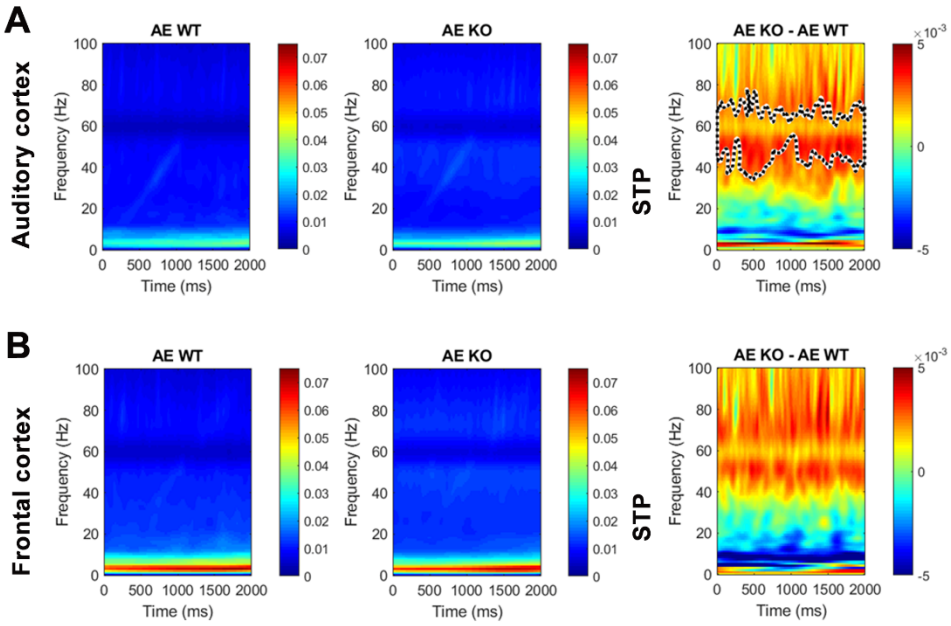

Fig. 6. Background Single Trial Power (STP) is increased in the gamma range during chirp stimulation in AC of AE KO mice
(A-B) Grand average matrices were calculated for each genotype (AE WT, left and AE KO, middle panels), and then average STP AE WT (n=6) value was subtracted from AE KO (n=15) value (right panels) for AC (A) and FC (B) Statistical cluster analysis reveals time x frequency bands that are significantly different between groups highlighted with bolded black borders

7. The MEA EEG experiments have been completed from AE adult mice (10 WT and 10 *Fmr1* KO). We found that adult KO resting low gamma power was significantly increased in the right temporal brain region compared to the WT controls, while there was no difference in all the other regions. Additionally, the chirp ITPC in adult KO was significantly increased in the right frontal and left temporal brain regions compared to the WT controls, while there was no difference in all the other regions. Lastly, the ERP power was significantly increased in the left and right frontal, right medial and right temporal brain regions of adult KO, while there was no difference in the left medial and left temporal brain regions. We will compare these data with SE mice with the different repetition rates using MEA EEG in year 3 of the project. The NE mice data are already published (Jonak et al., 2020).

8. We also tested the sensitivity of MEA EEG measurements to treatments using a PDE10A inhibitor and found phenotype and dose dependent effects and published these results in Jonak et al. (2021). These data set the stage in terms of group comparisons to test minocycline and sound exposure effects in year 3 of the project using MEA.
9. Graduate student Maham Rais was trained to setup and perform behavioral experiments on mice including open field, elevated plus maze, sociability and social novelty tests (Rais et al., In Review). Graduate student Xin Tao was trained to develop and perform a probabilistic reversal learning and social conditioned place preference test in mice. These behavioral tests will be used in year 3 of the project to determine efficacy of minocycline and sound exposure.

When examined in relation to the approved SOW, we accomplished the following:
Major task 1
Sub-task 1 – accomplished. We have recruited and trained a team of post-docs, graduate students and technicians to perform all experiments proposed.
Sub-task 2 –We have recorded EEGs and ERPs from sound exposed (SE) mice. The ERP data is already published (Kulinich et al., 2020). The EEG time x frequency analysis work has been completed in NE mice and published (Lovelace et al., 2018, 2020). The AE mice data is mostly collected and the SE data will be completed in the next reporting period. We have completed the AE MEA EEG data for electrophysiological analysis. The SE MEA EEG data will be completed in then ext reporting period.
Sub-tasks 3 – We have completed the 5 Hz and 1 Hz exposure rate data collection for histological analysis across groups.
Sub-task 4 – We have trained a graduate student to design and conduct behavioral experiments and this will be completed in year 3.

Major tasks 2 and 3 – We have already published (Lovelace et al., 2020) on the EEG responses following minocycline treatment in the Fmr1 KO mice (NE). Because minocycline can have other effects in the brain besides MMP-9 inhibition, we also tested and published the data on a specific MMP-9 inhibitor (Pirbhoy et al., 2020). Currently we have trained a graduate student (Katilynne Croom) to record EEGs and another graduate student (Xin Tao) to conduct behavioral results which will be obtained from mice treated with the combination of sound and minocycline in the next reporting period. This will cover both long term and acute effects of treatment combination.

Key Outcomes:
Publications
1. Jonak, C.R., Sandhu, M.S., Assad, S.A., Barbosa, J.A., Makhija, M. and Binder, D.K., 2021. The PDE10A Inhibitor TAK-063 Reverses Sound-Evoked EEG Abnormalities in a Mouse Model of Fragile X Syndrome. *Neurotherapeutics*, pp.1-13.
2. Pirbhoy PS, Jonak CR, Syed R, Perez PA, Wiley M, Hessamian K, Lovelace JW, Razak KA, DiPatrizio NV, Ethell IM, Binder DK. Increased 2-arachidonoyl-*sn*-glycerol levels normalize cortical responses to sound and improve behaviors in *Fmr1* KO mice. *JNDD (under review)*.
3. Rais M, Lovelace JW, Shuai XS, Woodard W, Bishay S, Estrada L, Sharma AR, Nguy A, Pirbhoy PS, Palacios AR, Nelson DL, Razak KA and Ethell IM. Postnatal interventions in excitatory neurons to shape cortical circuits in Fragile X syndrome. *Neurobiology of Disease (under review)*.

Reviews (included in Appendix):
1. Razak KA, Binder, DK and Ethell IM. Mechanisms and biomarkers of auditory hypersensitivity in Fragile X Syndrome. *Frontiers in Psychiatry – Child and Adolescent Psychiatry*. *In Pre*

What opportunities for training and professional development has the project provided?

We have trained 2 post-docs, 4 graduate students and 2 research technicians on the project aims. Post-docs, Patricia Pirbhoy and Anna Kulinich have been trained in EEG, MEA analyses, pharmacological treatment approaches, immunohistochemistry, histological analyses and behavioral analyses. They were each trained on analyzing complex EEG data and writing papers. Dr. Pirbhoy wrote and received her own grant funding from FRAXA, providing an important skillset for future success. They also first-authored papers during the reporting year as listed above. Graduate student Maham Rais has been trained in EEG, histological and behavioral analysis. She also successfully renewed an NIH F31 training grant for year 2. This prestigious and competitive fellowship will be a major aspect of professional development for Maham. She has now graduated and has started a post-doc position at Seattle Children's Hospital. Three other graduate students, Mawaheb Kassir, Xin Tao and Katilynne Croom have been recruited to be trained on these aims, particularly to develop behavioral analysis and EEG analysis tools. Research technician, Carrie Jonak, is trained to conduct MEA 30 channel EEG recordings. Research technician, Stephen Brookshire, has been trained in genotyping, mouse colony maintenance, histology and IHC analysis. He contributes by managing the resources so all trainees are optimally productive and the progress is maintained.

How were the results disseminated to communities of interest?

We have published 1 paper and 1 review article and 2 papers are in review during the reporting period (see above). Our usual conferences were not happening this year due to Covid19- related closures.

What do you plan to do during the next reporting period to accomplish the goals?

The main objective of year 3 is to complete the combined sound exposure + minocycline treatment during early development to identify benefits in terms of sensory, anxiety, social phenotypes. The mice are available and the students have been trained to accomplish this goal.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Our project is the first to test the idea that modifying sensory environment during development impacts autism specific behaviors and electrophysiological correlates. Although this is just the second reporting period, we have published more than 10 papers and 5 reviews during the funding period that have generated a novel understanding of pathophysiological mechanisms of FXS sensory hypersensitivity, novel therapeutic approaches and novel measurement and analysis methods. The unpublished data generated in this reporting period continue to point to differential regulation of PV/PNN inhibitory system in the cortex, mainly during the early developmental period, as a neural correlate of hypersensitivity. The 5Hz vs 1Hz repetition rate exposure produced different effects on PV/PNN and cFos expression, indicating specific effects on cortical mechanisms. These data suggest novel ways to think about therapeutics in FXS. The finding that MEA EEG responses are sensitive to pharmacological approaches (e.g., PDE inhibitor) has generated considerable interest in both academic and pharma companies who are developing other novel approaches.

What was the impact on other disciplines?

Our data that sound exposure during early development is beneficial has broad impact on sensory hypersensitivity in multiple disorders with sensory dysfunction. The PV/PNN system is implicated in a number of neurodevelopmental disorders including Rett Syndrome and Schizophrenia. Our finding that these cell types and their activities can be modulated by sound exposure with specificity for different repetition rates has major implications for treating multiple disorders.

What was the impact on technology transfer?

Our development of the 30 channel MEA EEG skull recordings from awake and freely moving mice has generated much interest in pharmaceutical companies to test developing drugs. The system is being used to test novel drugs (e.g., PDE inhibitor, Jonak et al., 2021). It was important to show sensitivity of the recordings to treatment effects, and that is indeed what was shown in the published article.

What was the impact on society beyond science and technology?

Nothing to report in this year annual progress report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

None

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

There was a short delay due to campus closures due to Covid19 in 2020. However, we were able to ramp up the research once campus and labs re-opened. We are delayed by ~3 months in where we expected to be in terms of data collection and trainee mentorship. We expect to make that up during the next reporting period, and are on track to complete the projects as proposed.

Changes that had a significant impact on expenditures

None to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

None

Significant changes in use or care of vertebrate animals

None

Significant changes in use of biohazards and/or select agents

None

6. PRODUCTS:

- **Publications, conference papers, and presentations**

  Journal publications.

Publications

1. Jonak, C.R., Sandhu, M.S., Assad, S.A., Barbosa, J.A., Makhija, M. and Binder, D.K., 2021. The PDE10A Inhibitor TAK-063 Reverses Sound-Evoked EEG Abnormalities in a Mouse Model of Fragile X Syndrome. *Neurotherapeutics*, pp.1-13.
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3. Rais M, Lovelace JW, Shuai XS, Woodard W, Bishay S, Estrada L, Sharma AR, Nguy A, Pirbhoy PS, Palacios AR, Nelson DL, Razak KA and Ethell IM. Postnatal interventions in excitatory neurons to shape cortical circuits in Fragile X syndrome. *Neurobiology of Disease (under review)*.

Reviews (included in Appendix):

2. Razak KA, Binder, DK and Ethell IM. Mechanisms and biomarkers of auditory hypersensitivity in Fragile X Syndrome. *Frontiers in Psychiatry – Child and Adolescent Psychiatry*. *In Press*.

Books or other non-periodical, one-time publications.

None

Other publications, conference papers and presentations.

Conference presentations:

1. Rais M., Lovelace J., Shuai X., Bishay S., Palacios A., Binder D., Razak K., Ethell I.M. (2020) Early postnatal FMR1 loss from cortical excitatory neurons elicits auditory processing deficits in a mouse model of FXS. CGNI meeting, Jan 2020. (Refereed, Electronic)*.
2. Ethell I.M. (2020) Sensory Hypersensitivity in Fragile X Syndrome: from genes to cells, circuits and behaviours. Symposium on Parvalbumin Cells in neuropsychiatric disorders: genetics, methabolism and extracellular environment, Federal European Neuroscience Societies (FENS) Forum in Neuroscience, July 2020. (Refereed, Invited, Electronic).

Seminar Presentations:

1. Razak KA (2021) Mechanisms and biomarkers of auditory hypersensitivity in Fragile X Syndrome', Perspectives in Neuroscience Seminar Series, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada.
2. Razak KA (2020). 'Mechanisms and biomarkers of sensory hypersensitivity in the Fmr1 knockout mouse', CSU-Dominguez Hills Seminar Series.
3. Razak KA and Binder DK. 'Mechanisms and biomarkers of sensory hypersensitivity in the Fmr1 knockout mouse', FRAXA Research Foundation Webinar Series.

Conferences organized:

Portera-Cailliau C, Ethell IM and Contractor A. Interneurons in Autism. 11/2020. International Virtual three-day conference with 300 registrants. https://sites.google.com/view/interneurons-in-autism-2020*

Websites:

None

Technologies or techniques

None

- **Inventions, patent applications, and/or licenses**

None

- **Other Products**

None

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Khaleel A. Razak*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Razak, along with co-PI and collaborator, designed experiments and trained post-docs and graduate students to collect and analyze EEG data and write publications.*
Funding Support:	*DOD*

Name:	*Iryna M. Ethell*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1.2*
Contribution to Project:	*Dr. Ethell, along with co-PI and collaborator, designed experiments and trained post-docs and graduate students to collect and analyze the biochemistry, immunohistochemistry and behavioral data and write publications.*
Funding Support:	*DOD*

Name:	*Devin K. Binder*
Project Role:	*Collaborator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Binder, along with PIs, designed experiments and trained post-docs and research technicians to collect and analyze the MEA EEG data and write publications.*
Funding Support:	*DOD*

Name:	*Stephen Brookshire*
Project Role:	*Lab Technician and Manager*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*8*
Contribution to Project:	*Mr. Brookshire is involved with genotyping and colony maintenance and obtaining histology data.*
Funding Support:	*DOD*

Name:	*Carrie Jonak*
Project Role:	*Research Associate and Manager*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*12*
Contribution to Project:	*Ms. Jonak is involved with genotyping and colony maintenance and obtaining all the MEA EEG data.*
Funding Support:	*DOD*

Name:	*Dr. Anna Kulinich*
Project Role:	*Post-doc*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6*
Contribution to Project:	*Dr. Kulinich is involved with mouse breeding and genotyping, designing the sound exposure chamber and controlling exposure of mice in this project and analyzing PV/PNN/cFos/MMP9 protein levels by immunohistochemistry and western blotting and EEG recordings .*
Funding Support:	*DOD and internal funds*

Name:	*Dr. Patricia Pirbhoy*
Project Role:	*Post-doc*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6*
Contribution to Project:	*Dr. Pirbhoy is involved with recording EEGs and performing behavioral experiments following early treatment of MMP9 inhibitors including SB-3CT and minocycline.*
Funding Support:	*FRAXA Foundation and Univ. of California Office of the President*

Name:	*Maham Rais*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6*
Contribution to Project:	*Ms. Rais is a doctoral student involved with IHC, behavior and EEG recordings of all aims.*
Funding Support:	*NIH F31*

Name:	*Xin Tao*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*4*
Contribution to Project:	*Ms. Tao is a doctoral student being trained to develop behavioral analysis in all aims*
Funding Support:	*DOD*

Name:	*Mawaheb Kassir*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2*
Contribution to Project:	*Ms. Kassir is a doctoral student being trained to develop EEG recordings. In particular, she is developing analytical tools to*

	analyze the complex MEA EEG datasets to examine cross regional interactions.
Funding Support:	*DOD*
Name:	*Katilynne Croom*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2*
Contribution to Project:	*Mrs. Croom is a doctoral student being trained to develop EEG recordings. In particular, she is trained to perform minocycline administration and sound exposure to study effects on EEG responses.*
Funding Support:	*DOD*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Razak KA
New Active Grants in the second reporting period – none have overlap with aims of the present grant

NSF (IOS2118607) (PIs: Saltzman, co-PI: Razak/Yamanaka/Trainor
Sensory Plasticity in Fathers
(total)

Period: 07/01/2021 – 06/30/2025.
Effort: 1.8 academic

NIH/NIA (1R01AG067073-01A1) (PIs: Metherate/Razak/Silver/Zeng)
Using nicotine to reverse age-related auditory processing deficits.
(total),
Period 01/2021 – 12/2026.
Effort: 1.0 summer

NIH (1 P50 HD104461-01) (P50 Center PIs: Erickson/Huber; UCR PIs: Binder/Razak)
Translational medicine and mechanistic studies of brain neurophysiology in Fragile X Syndrome
UCR component: 2.67 million (total)
Performance Period 09/25/2020 – 06/30/2025
Effort: 1.0 summer

Ethell IM

Nothing to report

Binder DK
New Active Grants in the second reporting period – none have overlap with aims of the present grant

NIH (1 P50 HD104461-01) (P50 Center PIs: Erickson/Huber; UCR PIs: Binder/Razak)
Translational medicine and mechanistic studies of brain neurophysiology in Fragile X Syndrome
UCR component: 2.67 million (total)
Performance Period 09/25/2020 – 06/30/2025
Effort: 3.6 calendar months

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

Attached following this page.