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TITLE: Uncovering Cellular and Network Mechanisms Underlying Cognitive Deficits in Fragile X Syndrome

PRINCIPAL INVESTIGATOR: Colgin, Laura

CONTRACTING ORGANIZATION: The University of Texas, Austin, TX

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

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November 2023	Final	15Jul2018-14Jul2023

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Uncovering Cellular and Network Mechanisms Underlying Cognitive Deficits in Fragile X Syndrome

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5b. GRANT NUMBER

W81XWH-18-1-0314

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

The University of Texas at Austin
100 E 24TH ST
Austin, TX 78712-0805

8. PERFORMING ORGANIZATION REPORT NUMBER

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

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

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11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The overarching goal of this work is to discover ways to counteract deficient neuronal coding of social stimuli, abnormal patterns of hippocampal gamma rhythms, and impaired social behaviors in a rat model of FXS (Fmr1 knockout rats, which we hereafter call "FXS rats"). During this period, we collected additional place cell recordings from area CA2 in wildtype control animals and FXS rats. We also collected additional olfactory habituation/dishabituation data from FXS rats and wildtype (WT) controls using social and non-social stimuli. We also made progress with our piloting of optogenetic experiments in Aim 2. We also began to test effects of intranasal administration of oxytocin on social exploratory behaviors and CA2 place cell coding. We also began to assess whether oxytocin receptor expression in hippocampal area CA2 differs between FXS rats and WT rats. Our results thus far are significant because they may provide a novel neuronal mechanism that contributes to aberrant social behavior deficits in Fragile X syndrome.

15. SUBJECT TERMS
Fragile X syndrome, place cells, hippocampus, CA2, gamma rhythms, oxytocin

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

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

The research addresses mechanisms underlying social memory deficits in Fragile X syndrome (FXS). The purpose is to discover ways to counteract deficient neuronal coding of social stimuli, abnormal patterns of hippocampal gamma rhythms, and impaired social behaviors in a rat model of FXS ("FXS rats"). The research spans multiple levels of observation, including investigation of mechanisms at the level of individual neurons, neuronal networks, and the behavioral level.

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

Fragile X syndrome, place cells, hippocampus, CA2, gamma rhythms, oxytocin

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

<u>*Specific Aim 1:*</u> Investigate whether behavioral deficits in FXS are accompanied by aberrant neuronal coding of social stimuli in hippocampal subfield CA2:

Major Task 1: Behavioral testing of control and FXS rats. Social

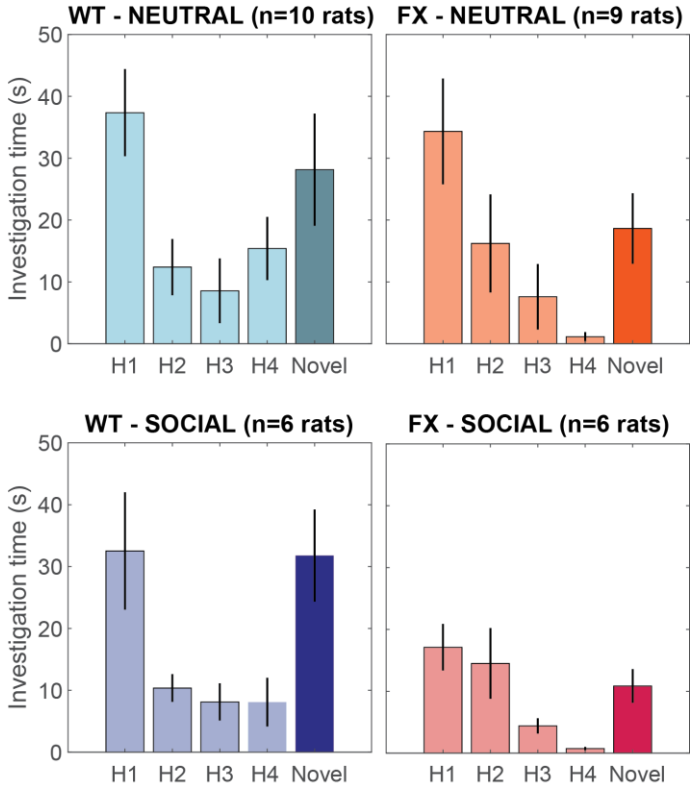

Fig. 1. FXS rats showed reduced exploration of social odors compared to wildtype (WT) rats, and olfactory habituation for neutral and social odors occurred in both WT and FXS rats. WT (left) and FXS (FX, right) rats performed olfactory habituation/dishabituation using non-social (top row) and social odors (bottom row). Both genotypes decreased odor sampling across 4 habituation sessions, and increased sampling of a novel odor in a subsequent session, for both non-social and social odors. FXS rats spent less time than WT rats investigating social odors.

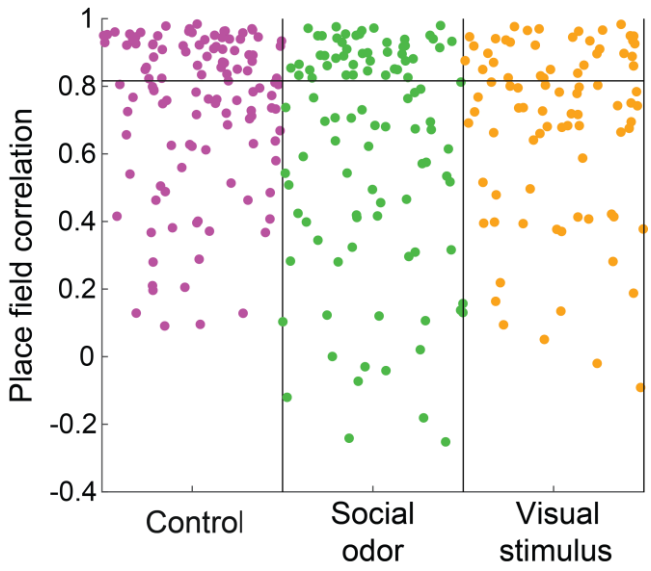

Fig. 2. CA2 place cells in WT rats respond to social odors. Scatterplots show place field correlations for individual place cells across control, social odor, and visual stimulus conditions. Place field correlations were significantly lower in the social odor condition compared to the control and visual stimulus conditions (repeated measures ANOVA: effect of condition, $F(2, 307) = 4.262$, $p = 0.015$; Bonferroni post-hoc tests: $p = 0.005$ for control vs. social odor condition) but did not differ between control and visual stimulus conditions ($p = 0.464$).

behavioral testing revealed that FXS rats have olfactory perception but show reduced exploration of social odors compared to non-social odors (Fig. 1).

Major Task 2: CA2 Place Cell Recordings.

Subtask 1: Recordings and analyses of CA2 place cell responses. Our results show that CA2 place cells in control rats respond to social stimuli, particularly to the olfactory component of social stimuli (Fig. 2). However, CA2 place cells in FXS rats show deficient responses to social odors compared to WT rats (Fig. 3).

Subtask 2: Recording and analyses of whether CA2 place cell responses to social stimuli in FXS are improved by increasing social neuropeptide levels. We did not obtain interpretable results for this Subtask because experimental methods did not work as expected in pilot experiments in control rats.

Subtask 3: Recording and analyses of whether CA2 place cell responses to social stimuli in FXS are improved by entrainment of theta-modulated fast gamma rhythms. We did not obtain interpretable results for this Subtask because experimental methods did not work as expected in pilot experiments in control rats. Specifically, our methods for theta frequency optogenetic stimulation of medial entorhinal cortex inputs to CA1 did not appear to reliably induce fast gamma rhythms in hippocampus.

Major Task 3: Assessing levels of social neuropeptides. This work was supposed to be completed in the early part of year 2 of the project. However, progress was greatly hindered by the ineffectiveness of commercially available antibodies for oxytocin receptors. We obtained an effective OXTR-2 antibody from Drs. Moses Chao and Rob Froemke at NYU. Their antibody allows co-immunostaining of oxytocin receptors together with the CA2 marker, PCP4, in rat brain tissue (Fig. 4). We have started assessing levels of social neuropeptides in CA2 of FXS and WT rats but were not able to complete this work before the project ended.

<u>*Specific Aim 2:*</u> *Test whether deficiencies in gamma rhythmic coordination of neuronal ensembles underlie social deficits in FXS.*

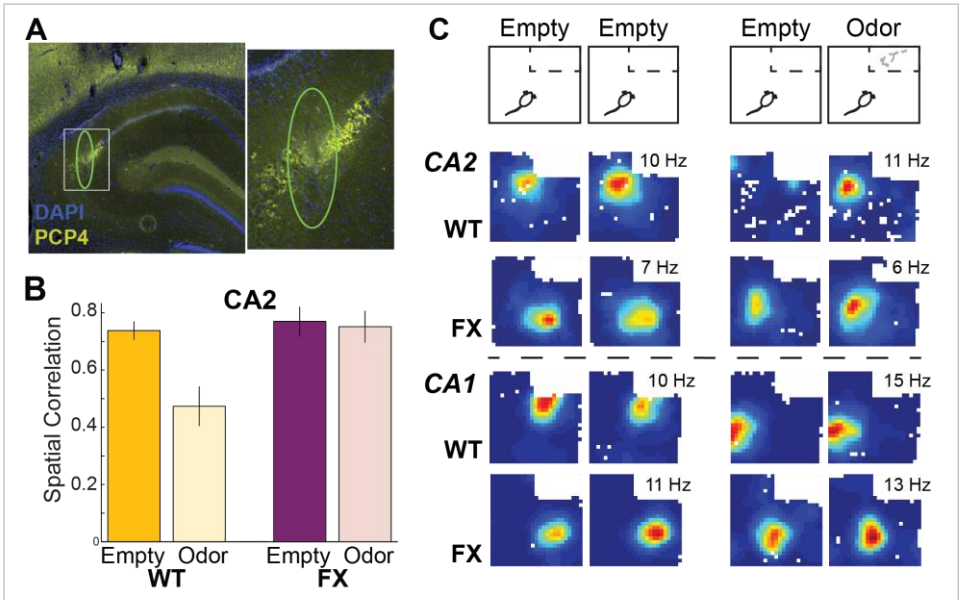

Fig. 3. CA2 place cells in FXS rats do not respond to social odors. A) Example immunostaining with CA2 marker (i.e., anti-PCP4 antibody) in yellow and DAPI nuclear staining in blue; oval indicates tetrode track in CA2. Boxed region from left shown magnified on right. B) Spatial correlations between CA2 place cell firing rate maps for control ("Empty") and social odor ("Odor") conditions. Spatial correlations in WT but not FXS (FX) rats were lower in the Odor condition (significant genotype x condition interaction effect ($F(1,117)=4.7$, $p = 0.03$); Post-hoc tests showed differences in spatial correlations between Empty/Control and Social Odor conditions for WT rats ($t(82)=3.9$, $p < 0.001$) but not FXS rats ($t(35)=0.24$, $p = 0.8$). C) Example CA2 and CA1 place cells from WT and FXS rats. Color-coded place cell firing rate maps are shown for control (Empty-Empty, left) and social odor comparisons (Empty-Odor, right). The CA2 place cell in the WT rat changed its firing pattern in response to social odor; the CA2 cell in the FXS rat did not alter its firing in response to social odor. CA1 place cells did not respond to social odors in WT or FXS rats. Color scale ranges from minimum (dark blue) to maximum (red) firing; maximal firing rate for each cell is shown inset.

Major Task 1: Investigating disturbances in the balance between hippocampal slow and fast gamma rhythms in FXS rats. This work was supposed to be completed by month 12. Data collection and analysis has been completed. However, drawing conclusions based on these results has been complicated by recent concerns raised in the theta-modulated gamma field about separating effects on gamma rhythms from effects that reflect changes in theta rhythm waveforms (e.g., Sheremet et al., 2019, Journal of Neurophysiology 121).

Major Task 2: Determine whether optical entrainment of theta-modulated fast gamma rhythms restores a healthy balance between hippocampal slow and fast gamma rhythms in FXS rats. This subtask was supposed to completed by month 36 but was delayed by piloting of optogenetics techniques in rats. Then, progress was further delayed by the university's pandemic response and associated restrictions on lab occupancy from March 2020 until July 2021, required rat colony culling in 2020, and restrictions on new rat orders in 2020-2021. After 2021, we were able to resume normal operations. However, our pilot data so far suggest that our methods for theta frequency optogenetic stimulation of medial entorhinal cortex inputs to CA1 do not reliably induce significant fast gamma rhythms in hippocampus. For this reason, we were unable to assess whether optical entrainment of theta-modulated fast gamma rhythms in the hippocampus alleviates deficits in social behaviors in FXS rats.

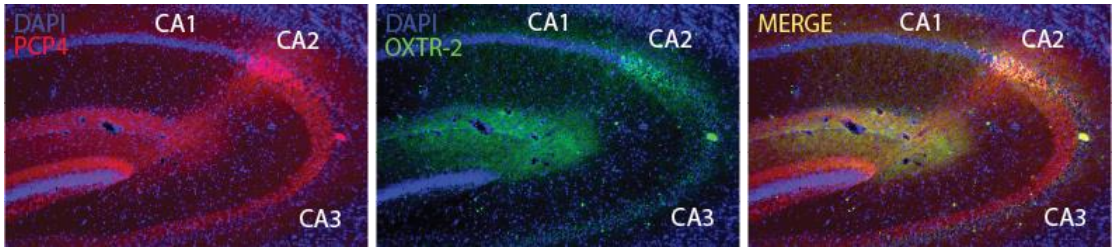

Fig. 4. Co-immunostaining of CA2 neurons and oxytocin receptors in an example WT rat. Example immunostaining for CA2 marker (i.e., anti-PCP4 antibody) in red, oxytocin receptors (i.e., OXTR-2 antibody) in green, and DAPI nuclear staining in blue.

What was accomplished under these goals?

Specific Aim 1. Aim 1 of the original award set out to investigate whether behavioral deficits in FXS are accompanied by aberrant neuronal coding of social stimuli in hippocampal subfield CA2: The work included behavioral testing of wildtype (WT) control and FXS rats (Major Task 1). Social exploratory behaviors were found to decrease in FXS rats compared to WT rats (e.g., see Fig. 1 and Okwubodu et al., Society for Neuroscience Abstracts 2021). Aim 1 also included CA2 place cell recordings in environments containing social stimuli and various control stimuli (Major Task 2, Subtask 1). Our results suggested that CA2 place cell responses to social stimuli were diminished in FXS rats compared to WT rats (see Fig. 3 and Robson et al., Society for Neuroscience Abstracts 2019). We are currently preparing our results for publication and expect to submit a paper reporting these results early next year.

Aim 1 of the original award also proposed to test whether administering the social neuropeptide oxytocin improves place cell responses to social stimuli in FXS rats (Major Task 2, Subtask 2). We were unable to obtain reliable results for administration of oxytocin in control rats, so we could not finish this Aim.

Specific Aim 1 of the original award also proposed to test whether optogenetic manipulations designed to entrain theta-modulated fast gamma rhythms would improve CA2 place cell responses to social stimuli in FXS rats (Major Task 2, Subtask 3). Much time was spent piloting the retrograde virus strategy to express channelrhodopsin-2 in medial entorhinal cortex inputs to CA1 in rats. Also, this subtask was greatly hindered by rat colony culling and rat ordering restrictions during the university's pandemic response in 2020-2021. These restrictions hindered pilot experiments because surplus rats for pilot studies were largely unavailable. All pandemic restrictions were lifted in July 2021, and we now have a technique that reliably produces desired expression patterns. However, our optogenetic protocol did not induce fast gamma rhythms in the hippocampus of WT rats, so we were unable to complete this Aim.

Specific Aim 1 of the original award also proposed to test whether expression levels of oxytocin receptors differ between WT and FXS rats (Major Task 3). This work was greatly hindered by ineffectiveness of commercially available oxytocin receptor antibodies. Fortunately, Drs. Moses Chao and Rob Froemke at NYU Langone Health generously shared their OXTR-2 antibodies with us. We use their antibody together with the CA2 marker, PCP4, in our rat brain tissue, and it works beautifully. We are now able to perform co-immunostaining of OXTR-2 and CA2 (see Fig. 2). We are currently evaluating whether expression levels of oxytocin receptors are

decreased in CA2 of FXS rats compared to WT rats. This work remains ongoing, but we expect to report results in a publication next year.

Specific Aim 2: The goal of Specific Aim 2 was to test whether deficiencies in gamma rhythmic coordination of neuronal ensembles underlie social deficits in FXS. Our initial results show that the balance between phase-locking of spike times to slow (~25-55 Hz) and fast (i.e., 65-100 Hz) gamma subtypes was abnormal in FXS rats (Specific Aim 2, Major Task 1). However, we have not yet obtained results for the second part of Specific Aim 2, namely determining whether optogenetic entrainment of theta-modulated fast gamma rhythms restores healthy patterns of slow and fast gamma rhythms in FXS (Specific Aim 2, Major Task 2). Major Task 2 involves the same optogenetic methods, and associated setbacks, described above for Specific Aim 1. Thus, this work was not completed. Also, valid concerns have recently been raised that effects related to theta-modulated slow gamma oscillations cannot be dissociated from theta dynamics in running rats, particularly at high running speeds (e.g., Sheremet et al., 2019, *Journal of Neurophysiology* 121). Thus, we cannot draw any definitive conclusions from our gamma results as of yet because they were obtained during active behaviors (i.e., theta-associated behaviors) and may reflect changes in theta waveforms rather than gamma-specific insights. We are currently developing new recording methods that we expect will allow us to interpret gamma effects during active behaviors.

To maximize impact of our work, we are planning to publish a complete report of differences in CA2 place cell responses to social stimuli, social behaviors, and CA2 oxytocin receptor expression between FXS and WT rats. We expect to submit a manuscript describing our findings early next year. Thus far, we have disseminated our results in talks and multiple poster presentations at various conferences. Poster presentations associated with published and citable abstracts are shown below:

E. ROBSON, A. J. MABLY, L. T. HEWITT, J. B. TRIMPER, L. L. COLGIN. Impaired CA2 place cell remapping in response to social olfactory stimuli in a rat model of fragile X syndrome. Society for Neuroscience Annual Meeting Abstracts 2019.
E. ROBSON, A. J. MABLY, L. T. HEWITT, P. DEMETROVICH, M. M. DONAHUE, L. L. COLGIN. The effects of social and neutral odors on hippocampal place cell activity. Society for Neuroscience Annual Meeting Abstracts 2021.
D. OKWUBODU, D. ASHADE, E. ROBSON, U. SALEEM, S. KIM, L. L. COLGIN. Testing for Odor Discrimination and Habituation in a rat model of Fragile X Syndrome. Society for Neuroscience Annual Meeting Abstracts 2021.

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

The project has provided training opportunities in hands-on neuroscience research to undergraduate researchers (e.g., Destiny Okwubodu), graduate students (e.g., Peyton Demetrovich), and postdoctoral researchers (e.g., Emma Robson). Trainees also traveled to conferences, therefore gaining professional development opportunities.

How were the results disseminated to communities of interest?
Poster presentations at conferences.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

This is the final report. Nothing to Report.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

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

We piloted a technique for co-immunostaining of oxytocin receptors and CA2, and we have shared the protocol with interested parties.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report.

Changes that had a significant impact on expenditures

Dr. Angel Lopez, the researcher who is leading the optogenetic studies, received a postdoctoral fellowship (UT Austin Provosts' Fellowship). So, she did not require salary support for part of this project. Peyton Demetrovich was funded as a teaching assistant for one semester, to fulfill the teaching requirements of his graduate program.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
None

Significant changes in use or care of human subjects

Not applicable

Significant changes in use or care of vertebrate animals

None

Significant changes in use of biohazards and/or select agents

None

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  E. ROBSON, A. J. MABLY, L. T. HEWITT, J. B. TRIMPER, L. L. COLGIN. Impaired CA2 place cell remapping in response to social olfactory stimuli in a rat model of fragile X syndrome. Society for Neuroscience Annual Meeting Abstracts 2019.
  E. ROBSON, A. J. MABLY, L. T. HEWITT, P. DEMETROVICH, M. M. DONAHUE, L. L. COLGIN. The effects of social and neutral odors on hippocampal place cell activity. Society for Neuroscience Annual Meeting Abstracts 2021.
  D. OKWUBODU, D. ASHADE, E. ROBSON, U. SALEEM, S. KIM, L. L. COLGIN. Testing for Odor Discrimination and Habituation in a rat model of Fragile X Syndrome. Society for Neuroscience Annual Meeting Abstracts 2021.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal;*

volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

  Nothing to report

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

  Technique for co-immunostaining of PCP4 (CA2 cell marker) and oxytocin receptors. Shared with Froemke Lab.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance

progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

  Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name:	Laura Colgin
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	**0000-0002-4853-8913**
Nearest person month worked:	2
Contribution to Project:	Dr. Colgin supervises the research project, leads the design of research studies, directs dissemination of results, and oversees the training of new personnel.
Funding Support:	

Name:	Emma Robson
Project Role:	Postdoctoral Fellow
Researcher Identifier (e.g. ORCID ID):	**0000-0001-5136-6158**
Nearest person month worked:	12
Contribution to Project:	Dr. Robson collected electrophysiological data, collected behavioral data, analyzed data, performed immunohistochemical analyses, helped train other researchers and disseminated results.
Funding Support:	

Name:	Sai Sirisha Dhavala
Project Role:	Research Engineering/Scientist Associate
Researcher Identifier (e.g. ORCID ID):	**0000-0003-2063-5372**
Nearest person month worked:	7.5
Contribution to Project:	Sirisha performs histological analysis of brain tissue. She also builds the recording devices for behavioral neurophysiology experiments. She also provided general technical support and performed rat husbandry duties.
Funding Support:	

Name:	Peyton Demetrovich
Project Role:	Graduate Research Assistant
Researcher Identifier (e.g. ORCID ID):	**0000-0003-1660-619X**
Nearest person month worked:	4
Contribution to Project:	He was learning techniques needed to perform behavioral neurophysiology experiments. He has also been assisting with behavioral training. He has also been helping Dr. Robson with behavioral neurophysiology data analysis. He piloted

	the oxytocin administration techniques and recently began his own independent behavioral neurophysiology recordings.
Funding Support:	This award, teaching assistantship from UT Austin

Name:	Margaret Donahue
Project Role:	Graduate Research Assistant
Researcher Identifier (e.g. ORCID ID):	**0000-0002-9356-3720**
Nearest person month worked:	1
Contribution to Project:	Ms. Donahue collected electrophysiological data, collected behavioral data, analyzed data, helped train other researchers and disseminated results.
Funding Support:	This award, NIH NRSA

Name:	Isabella Lee
Project Role:	Tech
Researcher Identifier (e.g. ORCID ID):	**0000-0001-7771-6531**
Nearest person month worked:	1.5
Contribution to Project:	Ms. Lee just recently started working in the lab. She has been learning to perform histological analysis of brain tissue. She has also been learning how to build the recording devices for behavioral neurophysiology experiments. She also provides general technical support (e.g.,

	ordering supplies) and performs rat husbandry duties
Funding Support:	

Name:	Ayomide Akinsooto
Project Role:	Tech-Part Time
Researcher Identifier (e.g. ORCID ID):	**0000-0003-2564-8367**
Nearest person month worked:	3
Contribution to Project:	Ms. Akinsooto built recording devices for the project. She was also training others how to build the recording devices for behavioral neurophysiology experiments. She was also assisting with general lab management.
Funding Support:	

Name:	Juan Enrique Villacres
Project Role:	Tech-Part Time
Researcher Identifier (e.g. ORCID ID):	**0000-0002-2102-2247**
Nearest person month worked:	1
Contribution to Project:	Mr. Villacres has been assisting with data analysis for the optogenetics experiment. He has also been assisting with rat behavioral training.
Funding Support:	

Name:	Destiny Okwubodu

Project Role:	Tech-Part Time
Researcher Identifier (e.g. ORCID ID):	**0000-0001-8904-9289**
Nearest person month worked:	3
Contribution to Project:	Ms. Okwubodu was running social behavioral experiments and assisting with data analysis. She was also assisting with rat behavioral training.
Funding Support:	This award. Nudelman Foundation Women in Neuroscience Fellowship

Name:	Angel Lopez
Project Role:	Postdoctoral Researcher
Researcher Identifier (e.g. ORCID ID):	**0000-0002-9219-2681**
Nearest person month worked:	4
Contribution to Project:	Dr. Lopez piloted virus injection techniques and piloted optogenetic stimulation experiments in behaving rats.
Funding Support:	UT Austin Provosts' Fellowship

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

Yes, we received two new grants, listed below.

Title: Modifying temporal coordination of hippocampal place cells through theta rhythmic stimulation of hippocampal inputs
Effort: 1.00 calendar
Agency: NIH-NIMH (R21MH129873)
Grants Officer: Monica Chavis, 6001 Executive Blvd, Rm 6200, MSC 9663 Bethesda, MD 20892-9663, monica.chavis@nih.gov
Performance Period: 04/2022 – 03/2024
Funding Level:
Goals & Specific Aims: Employing state-of-the-art multisite recording, optogenetic manipulation, and neuronal ensemble decoding techniques, we propose to test whether theta rhythmic stimulation of inputs to the hippocampus promotes theta coordination of neuronal ensembles that represent spatial memories and improves performance of a spatial memory task. Specific Aim 1: Determine whether theta-modulated stimulation of MEC inputs to CA1 activates theta-coordinated sequences of CA1 place cells; Specific Aim 2: Test whether theta-modulated stimulation of CA3 inputs to CA1 increases temporal compression of theta-coordinated sequences of CA1 place cells.
Overlap: None

Title: Investigating mechanisms underlying impaired social and spatial cognition in rodent models of Fragile X syndrome (R01MH131317)
Effort: 2.00 calendar
Agency: NIH-NIMH
Grants Officer: Robert Kirker, 6001 Executive Blvd, Rm 6200, MSC 9663 Bethesda, MD 20892-9663, robert.kirker@nih.gov
Performance Period: 08/2022-05/2026
Funding Level:
Goals & Specific Aims: This project will investigate the extent to which subcellular, cellular, circuit, and neuronal population mechanisms of social and spatial memory operations in the hippocampus are impaired in rodent models of FX. Specific Aim 1: Are inputs to CA2 impaired in FX during exploration of social stimuli?; Specific Aim 2: Are the cellular substrates associated with social memory impaired in FX?; Specific Aim 3: Is replay of CA1 place cell sequences impaired in FX?; Specific Aim 4: Are local CA1 inhibitory circuits altered in FX?
Overlap: None. Specific Aim 3 of this funded award investigates replay but not in novel environments, in contrast to the pending application/current proposal. Thus, there is no overlap between these awards.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Not applicable.

QUAD CHARTS: Not applicable

9. APPENDICES: None