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TITLE: The Relationship Between Brain Functioning, Behavior, and Microbiota in Autism Spectrum Disorder

PRINCIPAL INVESTIGATOR: Lisa Aziz-Zadeh, PhD

CONTRACTING ORGANIZATION: University of Southern California

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14. ABSTRACT Several studies have linked these GI issues to altered gut microbial composition, or dysbiosis, in ASD. Yet research has not yet clarified how dysbiosis may be related to the core features of ASD or to the symptom heterogeneity of this disorder. To our knowledge, no studies have investigated gut-microbiome-brain-behavior interactions in a single population of individuals with ASD to better understand the mechanisms of ASD heterogeneity. By examining these interactions, we aim to test the general hypothesis that alterations in gut microbial composition are correlated with structural and functional brain alterations, as well as with clinical and behavioral features of ASD. Building on the brain imaging and behavioral data generated by the Co-PI's R01 grant, we will acquire stool samples from all participants and characterize the composition, metagenome, and metabolome of their gut microbiome. We will relate individual differences across three continuums of symptoms (GI issues, social deficits, and sensory deficits) to activity in selected brain networks and microbiome-related data. The long-term goal of this research is to explain heterogeneity, develop biomarkers, and ultimately build individualized treatments for ASD directed at brain-gut-microbiome pathways.					
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1. INTRODUCTION: *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

While social communication deficits are considered the hallmark of autism spectrum disorder (ASD), comorbid gastrointestinal (GI) issues are common and impair quality of life in a large subset of affected individuals. Several studies have linked these GI issues to altered gut microbial composition, or dysbiosis, in ASD. Yet research has not yet clarified how dysbiosis may be related to the core features of ASD or to the symptom heterogeneity of this disorder. A growing number of studies support the concept that gut microbiota can signal to the brain by neural, endocrine, immune, and hormonal pathways. These microbial effects on the brain may modulate outputs in behavior, as well as in autonomic and neuroendocrine function. To our knowledge, no studies have investigated gut-microbiome-brain-behavior interactions in a single population of individuals with ASD to better understand the mechanisms of ASD heterogeneity. By examining these interactions, we aim to test the general hypothesis that alterations in gut microbial composition are correlated with structural and functional brain alterations, as well as with clinical and behavioral features of ASD. The long-term goal of this research is to explain heterogeneity, develop biomarkers, and ultimately build individualized treatments for ASD directed at alterations within the brain-gut-microbiome axis. Accomplishing our specific aims will not only allow us, for the first time, to better understand ASD from a whole body medical perspective, but it will also allow for better understanding of heterogeneity, diagnostic biomarkers, and potentially new forms of treatment for ASD (e.g., fecal microbial

transplantation, prebiotics, probiotics, and therapies aimed at specific gut microbes or their products).

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

Autism, Brain Imaging, fMRI, Neural Connectivity, Microbiome

STATEMENT OF WORK – 9/29/2017 (REV 04/19/2021)

3. MAJOR GOALS OF THE PROJECT

Specific Aim 1: To characterize the composition, metagenome, and metabolome of the gut microbiome in children with ASD.			
	Statement of Work Goal Completion Date	Actual Completion Date or Progress	
		Site 1: USC (LAZ)	Site 2: UCLA (EM)
Major Task 1: Prepare regulatory documents and research protocol for IRB Approval	1/19		
Milestone #1: <i>IRB approval received at both USC and UCLA</i>	11/18	9/18	N/A (Exempt)
Milestone #2: <i>Regulatory approval from DoD HRPO</i>	1/19	Approved 9/27/2019 1/27/2021 (COVID related changes)	N/A (Exempt)
Major Task 2: Hiring and training of study personnel on behavioral and clinical assessments and MRI/fMRI tasks	11/18	10/18	N/A
Milestone #2: <i>Study personnel achieves reliability on the ADOS and ADI-R</i>	11/18	12/18	N/A
Major Task 3: Collect gut microbiome data and brain	03/22		

Specific Aim 1: To characterize the composition, metagenome, and metabolome of the gut microbiome in children with ASD.

	Statement of Work Goal Completion Date	Actual Completion Date or Progress	
		Site 1: USC (LAZ)	Site 2: UCLA (EM)
		N/A	
Subtask 2: Run metabolomics analysis	2/21	N/A	Shipped for analysis on 06/21/22
Milestone #3: Present data at conferences and co-author manuscript on metagenomic and metabolic analysis in TD compared to children with ASD	5/21	1. Dr. Aziz-Zadeh presented at Microbiome First Virtual Summit 2. 2021 Chernikova, M.A., Flores, G.D., Kilroy, E., Labus, J.S., Mayer, E.A., Aziz-Zadeh, L. The brain-gut-microbiome system: Pathways and implications for autism spectrum disorder. Nutrients	1. Dr. Emeran presented at at Microbiome First Virtual Summit 2. 2021 Chernikova, M.A., Flores, G.D., Kilroy, E., Labus, J.S., Mayer, E.A., Aziz-Zadeh, L. The brain-gut-microbiome system: Pathways and implications for autism spectrum disorder. Nutrients

Specific Aim 2: To identify associations between altered brain network connectivity, gut microbial parameters, and behavior.

Major Task 5: Conduct functional (resting state) and anatomical connectivity (diffusion weighted imaging)			
Subtask 1: Resting state analyses (data preprocessing and QC, seed-to-voxel connectivity, complex network analysis and machine learning approaches)	2/21	Analyzed as of 08/22	Analyzed as of 08/22
Milestone #4: Present data at conferences and co-author manuscript on correlations between resting	5/21	Delayed due to COVID-19	Delayed due to COVID-19

Specific Aim 1: To characterize the composition, metagenome, and metabolome of the gut microbiome in children with ASD.

	Statement of Work Goal Completion Date	Actual Completion Date or Progress	
		Site 1: USC (LAZ)	Site 2: UCLA (EM)
<i>state connectivity, microbiome- related data, and behavioral data</i>		Expected to complete Spring 2023	Expected to complete Spring 2023
Subtask 2: DTI analyses (deterministic and probabilistic tractography, voxel-based analysis, complex network analysis; machine learning approaches)	2/21	Analyzed as of 08/22	Analyzed as of 08/22
Milestone #5: Present data at conferences and co-author manuscript on correlations between DTI analyses, microbiota related data, and behavior	5/21	Delayed due to COVID-19 Expected to complete Spring 2023	Delayed due to COVID-19 Expected to complete Spring 2023
Major Task 6: Conduct correlations brain network analyses, gut microbial parameters, and behavior			
Subtask 1: Analyze behavioral data	12/20	Completed as of 06/22	
Subtask 2: Conduct correlations between behavioral data, microbiome-related data, and behavioral data	12/20	Delayed due to COVID-19 Expected to complete in Fall 2022	Delayed due to COVID-19 Expected to complete in Fall 2022
Milestone #6: Present data at conferences and co-author manuscript on correlations on brain resting state connectivity, microbiota related data, and behavior	5/21	Delayed due to COVID-19 Expected to complete in Spring of 2023	Delayed due to COVID-19 Expected to complete in Spring of 2023

Specific Aim 1: To characterize the composition, metagenome, and metabolome of the gut microbiome in children with ASD.

	Statement of Work Goal Completion Date	Actual Completion Date or Progress	
		Site 1: USC (LAZ)	Site 2: UCLA (EM)
Major Task 7: Conduct machine-learning and neural network analyses (classification, ensemble clustering) of the combined microbiota, behavioral, and MRI data to identify microbial features and connectivity patterns that predict clinical diagnosis and heterogeneity within ASD	REMOVED FROM SOW DUE TO COVID-19	N/A	N/A
Milestone #7: Present data at conferences and co-author manuscript based on machine learning analyses combining microbiota, behavioral and structural MRI data that can better understand heterogeneity within ASD and predict clinical diagnosis	REMOVED FROM SOW DUE TO COVID 19	N/A	N/A
Specific Aim 3: To identify associations between altered brain activation patterns and gut microbial parameters			
Major Task 8: Conduct fMRI analyses of emotional face processing in all participants	12/20	Completed as of 07/22	
Major Task 9: Conduct correlations between fMRI analysis results and gut microbial parameters	12/20	Delayed due to COVID-19 Expected completion by the end of Fall 2022	Delayed due to COVID-19 Expected completion by the end of Fall 2022
Milestone #8: Present data at conferences and co-author manuscript on correlations on fMRI data during emotional face	5/21	Delayed due to COVID-19	Delayed due to COVID-19

Specific Aim 1: To characterize the composition, metagenome, and metabolome of the gut microbiome in children with ASD.

	Statement of Work Goal Completion Date	Actual Completion Date or Progress	
		Site 1: USC (LAZ)	Site 2: UCLA (EM)
<i>processing and microbiota related data</i>		Expected completion by Spring 2023	Expected completion by Spring 2023
Major Task 10: Conduct association network analyses between fMRI data and gut microbial parameters and behavioral data	12/20	Delayed due to COVID-19 Expected completion by the end of Fall 2022	Delayed due to COVID-19 Expected completion by the end of Fall 2022
Milestone #9: Present data at conferences and co-author manuscript on correlations on fMRI data during emotional face processing, microbiota related data, and behavioral data	5/21	Delayed due to COVID-19 Expected completion by Summer 2023	Delayed due to COVID-19 Expected completion by Summer 2023
Major Task 11: Conduct machine-learning analyses (classification, ensemble clustering) of the combined microbiota, behavioral and task based fMRI data to identify microbial features and activation patterns that predict clinical diagnosis and heterogeneity within ASD	REMOVED FROM SOW DUE TO COVID-19	N/A	N/A
Milestone #10: Present data at conferences and co-author manuscript based on machine learning analyses combining microbiota, behavioral and task based fMRI data that can better understand heterogeneity within ASD and predict clinical diagnosis	REMOVED FROM SOW DUE TO COVID-19	N/A	N/A

4. 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.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Specific Aim 1: To characterize the composition, metagenome, and metabolome of the gut microbiome in children with ASD

Major Task 1: Prepare regulatory documents and research protocol for IRB Approval

- *Milestone # 1: IRB approval received at both USC and UCLA*
- *Milestone #2: Regulatory approval from DoD*

IRB has been approved by USC and DoD.

Major Task 2: Hiring and training of study personnel on behavioral and clinical assessments and MRI/fMRI tasks

- *Milestone # 1: Study personnel achieves reliability on the ADOS and ADI-R*

This milestone has been completed.

Major Task 3: Collect gut microbiome data and brain imaging from typically developing

Subtask 1: Complete data collection of the 40 ASD and 40 TD participants from ongoing R01 study.

- *Milestone #1: Collect MRI data from these participants (using funds from R01 study)*

This milestone has been completed.

Subtask 2: Recruit 20 additional ASD and 20 additional TD participants in each group (using new funds from current proposal).

- *Milestone #2:* Collect microbiota data from these participants (using new funds from current proposal)

This milestone has been completed.

Major Task 4: Conduct metagenomic and metabolomics of the gut microbiome

Subtask 1: Run shot-gun metagenomics

Subtask 2: Run metabolomics

These tasks are in process: UCSD (Dr. Knight's microbiome lab) is currently conducting shot-gut metagenomics for us and Metabalon is currently conducting metabolomics for us.

- *Milestone #1:* Present data at conferences and co-author manuscript on metagenomic and metabolic analysis in TD compared to children with ASD

Preliminary data from this project and theory papers related to this project were delivered at 6 different conferences (listed below). Dr. Aziz-Zadeh presented preliminary data from this project at 2 conferences, Dr. Mayer at 2 separate conferences, and an undergraduate volunteer in the lab at 1 conference.

We have written a review article about brain gut microbiome interactions in ASD, which was published in *Nutrients* December, 2021.

Specific Aim 2: To identify associations between altered brain network connectivity, gut microbial parameters, and behavior.

Specific Aim 3: To identify associations between altered brain activation patterns and gut microbial parameters

Resting state, DTI, functional MRI and behavioral data analysis have been completed and we plan to complete correlations between behavioral and microbiome-related data this Fall. We are delayed in completing all of the aims in the timeframe listed above due to COVID-19. Therefore, we plan to present the data by Spring 2023.

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

This current project has provided several training and professional development opportunities for undergraduate research assistants, graduate students, occupational therapy doctoral residents, and post-graduate trainees who have worked on this project.

Undergraduate Research Assistant Training: Several undergraduate research students have been trained in data collection and recruitment protocols as part of this project at USC. Specifically, Ariel Pruyser (Loyola Marymount University), Genesis Flores (California State Polytechnic University, Pomona) and Michelle Chernikova (Loyola Marymount University), all enrolled through the University of Southern California (USC) Diversity, Inclusion & Access (DIA) Jumpstart fellowship, have been receiving ongoing training in this project since June 2020. Additionally, Samantha Antekeier joined the team as a DIA student in June 2021 and Christine Figueroa in June 2022. All DIA Jumpstart fellows received training and education in working with those with autism spectrum disorders (ASD), fMRI protocol and microbiota data acquisition and analysis, in addition to general training in the day-to-day activities associated with scientific research. The trainees were trained in designing and developing parent surveys related to the project's aims. Additionally, the current funding and associated projects have provided Ms. Pruyser, Ms. Flores, Ms. Antekeier and Ms. Chernikova with training in scientific writing and principles of scientific data dissemination. Ms. Pruyser, Ms. Flores, and Ms. Chernikova presented posters at the 2020 DIA Scholar symposium at USC. Both Ms. Chernikova and Ms. Antekeier completed posters presented at the 2021 DIA Scholar symposium at USC. Ms. Pruyser is a McNair scholar and used data from the lab for her presentation on how embodied communication is reduced during emotion experience description in children with ASD at the 2020 UCLA Virtual National McNair conference. Ms. Flores used data collected as part of the project for her final presentation on the preliminary results of microbiome-gut-brain axis influence on emotion processing in typically developing children. Ms. Chernikova, Ms. Pruyser, and Ms. Flores also completed a poster presentation titled Caregiver and Youth Inter-Rater Assessment Agreement in Autism Spectrum Disorder and Developmental Coordination Disorder at the Association for Psychological Science (APS) 2021 Virtual Convention. In November 2021, Ms. Chernikova and Ms. Flores submitted a manuscript entitled “The Brain-Gut-Microbiome System: Pathways and Implications for Autism Spectrum Disorder” which was then published in *Nutrients* in December 2021. Additionally, another undergraduate researcher at the USC laboratory, Gabriel Abrams, used data collected on this project to complete his undergraduate thesis in 2021 with help from graduate students and postdocs. In June of 2022, Mr. Abrams submitted a manuscript comparing praxis errors in children with autism and developmental coordination disorder to the *Journal of the American Medical Association*.

In Spring of 2022, Fernanda Loureiro, Tom Williamson, Taran Gupta, and Brittany Bynum joined as volunteer research assistants. Mr. Gupta (University of Southern California) received general training in the day-to-day activities associated with scientific research. Ms. Bynum (University of Southern California) has focused on MRI data pre-processing and analysis with the guidance of PhD candidate, Aditya Jayashankar. Both Mrs. Loureiro and Mr. Williamson have been receiving guidance in scientific writing and principles of scientific data dissemination, focusing on different areas of research with support from PhD student, Sofronia Ringold, and collaborators.

Master's Level Graduate Training: Lamoni Lucas, Trinh Nguyen, and Corinne Archer, master's students in the USC Occupational Therapy program, were awarded research assistant placements to work with Dr. Aziz-Zadeh's lab on this project for the academic years 2019 – 2021. Ms. Nguyen's award was renewed for 2021 – 2022, alongside Gregory Natt and Nandita Raman. Additionally, Chantal Sotomayor, Ka Ki Tam, Vanessa Mesa, and Tristenne Ocampo joined the team as volunteers. They were trained in ASD, microbiota, diet questionnaires, participant recruitment strategies, psychological assessments and functional Magnetic Resonance Imaging

(fMRI) data collection. They also received training in professional development and scientific writing and data dissemination through mentorship with postdocs and OT residents in the lab.

PhD Graduate Training: Sofronia Ringold began her graduate program in August 2021 and Aditya Jayashankar in August of 2018. Sofronia, gained experience with study management and oversight of undergraduate research assistants as well as training in administering behavioral assessments and functional Magnetic Resonance Imaging (fMRI) data collection and analysis, with the support of Aditya. Sofronia published an abstract at USC’s Research Day and the International Society for Research on Emotion (ISRE), and Aditya published an abstract in ISRE and the International Society for Autism Research (INSAR). Sofronia submitted a manuscript related to sensory processing in children with developmental coordination disorder to a special issue of *Brain Science* in July, 2022. Aditya additionally submitted a manuscript entitled “Feeling disgusted: Disgust processing and potential relationships with behaviors in youth with ASD” which is currently under review.

Occupational Therapy Doctoral Training: Michelle Canales (2020-2021), Riley McGuire (2021 – 2022), and Nandita Raman (2022 – 2021) Occupational Therapy Doctoral Residents at USC gained training and experience in lab protocols specific to this project, as well as educational and professional development. They received training on ASD, microbiota data collection, clinical assessments, ASD participant recruitment, as well as general training in the day-to-day activities associated with scientific research including internal review board submissions and maintenance, database software (RedCap), and research lab management.

Professional Development and Post-Graduate Training: Additional training and professional development has been provided to Dr. Aziz-Zadeh, PI of this project and Dr. Emily Kilroy, a postdoctoral trainee on the project. As a result of this award, Dr. Aziz-Zadeh and Dr. Kilroy have continued to receive training in (a) sensory processing assessments in young children with ASD, (b) microbiota research through online courses, conferences, and through meetings with UCLA collaborators (c) microbiota data acquisition and analysis (c) mentorship of undergraduate and graduate students, and (d) study and personnel management. All of the training listed above resulted in increased knowledge and skills pertaining to the project’s aims. Additionally, Dr. Aziz-Zadeh has attended conferences and seminars relating to state-of-the-art microbiota analysis and research findings. She additionally mentored four undergraduate Diversity, Inclusion, and Access Jumpstart Scholar Interns over the past two summers and worked with them specifically on projects relating to the current project (i.e., refining assessment protocols and writing a review manuscript of current ASD and microbiota literature). Furthermore, she has spent one-on-one time working with the PI, Lisa Aziz-Zadeh, furthering her professional development in scientific grant writing and principles of scientific data dissemination. Emily completed her postdoctoral training in December 2021.

The UCLA Team will utilize training of post-docs in the coming year (2022-23) during data analysis and manuscript write-up phases.

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.”

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

As stated above, we originally planned to complete data acquisition by the end of September 2020. However, we were unable to collect data from any participants from March 2020 – January 2021 due to COVID-19 which significantly impacted our timeline. However, all data acquisition is currently complete, all behavioral and brain imaging analysis is now complete, and we will begin correlation analysis as soon as the microbiome analysis is complete. We plan to finish running correlations and association network analyses by Fall 2022 so that we can proceed with manuscript writing and presenting our findings in Spring and Summer of 2023.

5. IMPACT: *Describe 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?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report at this time.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report at this time.

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report at this time.

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Dr. Aziz-Zadeh delivered a talk at the Help Group Annual Symposium (2019) which includes scientists, practitioners, clinicians, and individuals and their families with autism. The title of the talk was “The brain, the microbiome, and behavior in autism”, and it was well received, with the public very much interested in this topic, especially families with individuals with autism, as the PIs received multiple emails following the symposium from audience members. Dr. Aziz-Zadeh also delivered a keynote talk at the Annual Meeting of Neuroscience National Research Council in Italy (2020) which included discussion on and preliminary data from this project. She also delivered a talk at the STAR Institute Summit which is a Summit attended by families with autism, practitioners, and researchers.

Dr. Mayer delivered several talks on gut microbiome brain interactions including the following: International Association for Polyphenol Research Conference, London, July 13, 2020 (Title: Gut Brain Connections to Behaviors in Humans); MENLA Virtual Symposium “Weeding, Feeding and Seeding”, Jan 21, 2021 (Title: The Gut Immune Connection); Columbia University Digestive, Liver Disorders Research Center Seminar on June 2, 2021 (Title: The Brain Gut Microbiome System – Implications for GI Disorders); NuRhoPsi Neuroscience Symposium, Atlanta, April 9, 2021 (Title: The Gut Immune Connection and How it Affects the Brain); Oregon Society for Neuroscience Chapter, April 4, 2021 (Title: the Gut Immune Connection and How It Affects The Brain).

Both Dr. Aziz-Zadeh and Dr. Mayer delivered talks at the Microbiome First, Virtual Conference in Spring of 2022, and they were related to the current study. Dr. Aziz-Zadeh further discussed the behavioral and brain imaging findings from this study at International Society for Autism Research Annual Meeting in Austin, TX. Further Dr. Labus presented at the Alzheimer’s Association International Conference in 2022.

Student presentations at conferences in the past year directly related to this work also include the following:

- 2022 Ringold, S. *, Jayashankar, A. *, Kilroy, E. *, McGuire, R. *, Butera, C. *, **Aziz-Zadeh, L.** Personality and social touch in typically developing and children with ASD. *USC Herman Ostrow School of Dentistry Research Day*, Los Angeles, CA.
- 2022 Ringold S. *, Jayashankar, A. *, Kilroy, E. *, McGuire, R. *, Butera, C. *, **Aziz-Zadeh, L.** Enhanced perception is related to alexithymia differentially in typically developing children and children with autism spectrum disorder (ASD). *International Society for Research on Emotion (ISRE) Conference*, Los Angeles, CA.
- 2022 Jayashankar, A. *, Kilroy, E. *, Butera, C. *, Harrison, L. *, Ringold, S. *, McGuire, R. *, **Aziz-Zadeh, L.** Anterior insula reactivity is associated with disgust propensity in children with Autism Spectrum disorder (ASD). *International Society for Research on Emotion (ISRE) Conference*, Los Angeles, CA.
- 2022 Jayashankar, A. *, Kilroy, E. *, Ringold, S. *, McGuire, R. *, **Aziz-Zadeh, L.** Physical disgust processing in children with autism spectrum disorder (ASD) during

observation of rotten foods. *International Society for Autism Research (INSAR) Annual Meeting*, Austin, TX.

- 2022 Butera, C. *, Ring, P. *, Harrison, L. *, Jayashankar, A. *, Sideris, J., Kilroy, E. *, Cermak, S., Chernikova, M., Kaplan, J., **Aziz-Zadeh, L.** Impact of sensory functioning on school performance and social-emotional outcomes in ASD. *International Society for Autism Research (INSAR) Annual Meeting*, Austin, TX.

Finally, undergraduate student Genesis Flores, who spent the summer of 2020 in Dr. Aziz-Zadeh's lab as part of the Diversity, Inclusion, and Access Program at USC and continued in the lab till June 2022, gave a virtual seminar on potential involvement of the gut-microbiome brain axis on emotional expressions in autism. All the talks were well received and were followed by ample discussion and interest.

6. 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

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report.

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.

As previously noted, we have experienced a year of delays from the ban on running in person participants during the first year of the COVID-19 pandemic. Nevertheless, we have acquired a no-cost extension and we anticipate completion of the project goals in the timeline outlined above. We have analyzed all the behavioral and neuroimaging data, have submitted all our stool samples for microbiome analysis, and the majority of our remaining work is to run statistical analyses on all data together and write and submit manuscripts.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

We are carrying over funds that we will use to complete data analysis and publish data.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report.

7. 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.

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).*

Forthcoming manuscripts (behavioral and brain imaging data from the current study):

1. Kilroy, E., Gerbella, M., Cao, L., Molfese, P., Butera, C., Harrison, L., Jayashankar, A., Rizzolatti, G., Aziz-Zadeh, L. Specific tractography differences in autism: Comparing autism spectrum disorder and developmental coordination disorder. In Review at *Nature: Scientific Reports*.
2. Butera, C., Kaplan, J.T., Kilroy, E., Harrison, L., Jayashankar, A., Loureiro, F., Aziz-Zadeh, L. The relationship between alexithymia, interoception, and neural functional connectivity during facial expression processing in autism spectrum disorder. In Review at *Neuropsychologia*.
3. Jayashankar, A., Aziz-Zadeh, L. Feeling disgusted: Disgust processing and potential relationships with behaviors in youth with ASD. In Review at *Autism Research*.
4. Ringold, S., McGuire, R., Jayashankar, A., Kilroy, E., Ring, P., Butera, C., Harrison, L., Aziz-Zadeh, L., Cermak, S. Sensory sensitivities in developmental coordination disorder as compared to autism. In Review at *Brain Sciences*.
5. Abrams, G., Jayashankar, A., Kilroy, E., Butera, C., Harrison, L., Ring, P., Cermak, S., Aziz-Zadeh, L. Motor Performance, praxis, and social skills in autism spectrum disorder and developmental coordination disorder. In Review at *Journal of Autism and Developmental Disorders*.

6. Butera, C., Delafield-Butt, J., Lu, S., Sobota, K., McGowan, T., Harrison, L., Kilroy, E., Jayashankar, A., Aziz-Zadeh, L. Motor signature differences between autism spectrum disorder and developmental coordination disorder, and their neural mechanisms. In preparation.

Published papers (behavioral and brain imaging data from the current study):

7. Kilroy, E., Ring, P., Hossain, A., Nalbach, A., Butera, C., Harrison, L., Jayashankar, A., Vigen, C., & Aziz-Zadeh, L. (2022). Motor performance, praxis, and social skills in autism spectrum disorder and developmental coordination disorder. *Autism Research*. In Press.
8. Harrison, L. A., Kats, A., Kilroy, E., Butera, C., Jayashankar, A., Keles, U., & Aziz-Zadeh, L. (2021). Motor and sensory features successfully decode autism spectrum disorder and combine with the original RDoC framework to boost diagnostic classification. *Scientific reports*, *11*(1), 1-16.
9. Chernikova, M. A., Flores, G. D., Kilroy, E., Labus, J. S., Mayer, E. A., & Aziz-Zadeh, L. (2021). The brain-gut-microbiome system: pathways and implications for autism spectrum disorder. *Nutrients*, *13*(12), 4497.
10. Kilroy, E., Harrison, L., Butera, C., Jayashankar, A., Cermak, S., Kaplan, J., Williams, M., Haranin, E., Bookheimer, S., Dapretto, M. & Aziz-Zadeh, L. (2021). Unique deficit in embodied simulation in autism: An fMRI study comparing autism and developmental coordination disorder. *Human brain mapping*, *42*(5), 1532-1546.
11. Butera, C., Ring, P., Sideris, J., Jayashankar, A., Kilroy, E., Harrison, L., Cermak, S. & Aziz-Zadeh, L. (2020). Impact of sensory processing on school performance outcomes in high functioning individuals with autism spectrum disorder. *Mind, Brain, and Education*, *14*(3), 243-254.

Published papers related to the gut-microbiome (though not from the current data set):

12. LaPelusa, M., Donoviel, D., Branzini, S.E., Carlson, P.E., Jr, Culler, S., Cheema, A.K., Kaddurah-Daouk, R., Kelly, D., de Cremoux, I., Knight, R., Krajmalnik-Brown, R., Mayo, S.L., Mazmanian, S.K., Mayer, E.A., Petrosino, J.F, Garrison, K. (2021) Microbiome for Mars: surveying microbiome connections to healthcare with implications for long-duration human spaceflight, virtual workshop. *Microbiome*. PMID: 33397500
13. Frith, J., Grangwisch, J.E., Borisini, A. Wootton, R.E., Mayer, E.A. (2020) Food and mood: How do diet and nutrition affect mental well being? *BMJ*. PMID: 32601102.
14. Bonaz, B., Lane, R.D., Oshinsky, M.L., Kenny, P.J., Sinha, R., Mayer, E.A., Critchley, H.D. (2020) Diseases, Disorders, and Comorbidities of Interoception. *Trends Neuroscience*. PMID: 33378656
15. Bonaz B, Lane RD, Oshinsky ML, Kenny PJ, Sinha R, Mayer EA, Critchley HD. (2020) Diseases, Disorders, and Comorbidities of Interoception. *Trends Neuroscience*. PMID: 33378656
16. Kilroy, E., Cermak, S. A., & Aziz-Zadeh, L. (2019). A review of functional and structural neurobiology of the action observation network in autism spectrum disorder and developmental coordination disorder. *Brain Sciences*, *9*(4), 75.
17. Osadchiy, V., Martin, C.R., Mayer, E.A. (2019) Gut microbiome and modulation of CNS function. *Comp Physiology*. PMID: 31853944
18. Bhatt, R.R., Gupta, A., Mayer, E.A., Zeltzer L.K. (2019) Chronic pain in children: Structural and resting state functional brain imaging within a developmental perspective. *Pediatric Research*. PMID: 31791045.

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).

1. Ringold, S., Jayashankar, A., Kilroy, E., McGuire, R., Butera, C., Aziz-Zadeh, L. Personality and Social Touch in Typically Developing and Children with ASD. (2022) USC Herman Ostrow School of Dentistry Research Day. Los Angeles, California.
2. Ringold S., Jayashankar, A., Kilroy, E., McGuire, R., Butera, C., Aziz-Zadeh, L. Enhanced Perception is Related to Alexithymia Differentially in Typically Developing Children and Children with Autism Spectrum Disorder (ASD). (2022) International Society for Research on Emotion (ISRE) Conference. Los Angeles, CA, United States.
3. Jayashankar, A., Kilroy, E., Butera, C., Harrison, L., Ringold, S., McGuire, R., Aziz-Zadeh, L. Anterior insula reactivity is associated with disgust propensity in children with Autism Spectrum disorder (ASD). (2022) International Society for Research on Emotion (ISRE) Conference. Los Angeles, CA, United States.
4. Jayashankar, A., Kilroy, E., Ringold, S., McGuire, R., Aziz-Zadeh, L. Physical disgust processing in children with Autism Spectrum Disorder (ASD) during Observation of Rotten Foods. (2022) International Society for Autism Research (INSAR) Conference. Austin, TX, United States.
5. Butera, C., Ring, P., Harrison, L., Kilroy, E., Jayashankar, A., Sideris, J., Cermak, S., Chernikova, M., Kaplan, J., Aziz-Zadeh, L. Impact of Sensory Functioning on School Performance and Social-Emotional Outcomes in ASD. (2022) International Society for Autism Research Annual Meeting. Austin, Texas.
6. Labus, J.S., Tun, G., Kilpatrick, L.A., Rao, S.C., Mayer, E.A., Tillisch, K. Neuroimaging and Biomarkers in functional gastrointestinal disorders: What scientists and clinicians need to know about basic neuroimaging, biomarkers, microbiome, gut, and brain interactions. In: Rao, SC, Lee YY, Ghosal, UC (eds.) Clinical and Basic Neurogastroenterology and Motility (Ch. 3. Pp. 31-53) Academic Press, Elsevier Inc., 2020.
7. Mayer, E.A. The Gut-Immune Connection: The Invisible link between the food we eat and the microbes within us -- How we can take back our health. Harper & Collins. June, 2021.

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.*

1. Aziz-Zadeh, L. (2022) Understanding dissimilar others. NeuroLeadership Annual Summit, Virtual.
2. Aziz-Zadeh, L. (2022) Motor processing in autism (behavioral and neural) and the relationship between motor and social processing. International Ayres Sensory Integration® Annual Congress, Redondo Beach, CA.
3. 2022 Aziz-Zadeh, L. (2022) Brain-gut-microbiome system: Pathways and implications for autism spectrum disorder. Microbiome First: Pathway to Sustainable Healthcare Summit, Virtual.
4. 2021 Aziz-Zadeh, L., (2021) Rock, David. Managing humans: The neuroscience of empathy. NeuroLeadership Institute: Your Brain at Work Live, Virtual.
5. 2022 Aziz-Zadeh, L. Unique motor differences in ASD and their structural and functional neurological basis. International Society for Autism Research Annual Meeting, Austin, TX

6. Aziz-Zadeh, L. (2020) Understanding the neural basis of social, motor, and microbial deficits in autism. Keynote Speaker, *Annual Meeting of Neuroscience National Research Council, Italy* [online live seminar due to COVID-19]
7. Aziz-Zadeh, L. (2020) Toward A Better Understanding of Social & Motor Deficits in Children with Autism Speaker at STAR Institute Virtual Summit: Sensory Processing in Autism
8. Aziz-Zadeh, L. (2020). Sensorimotor and gut differences in ASD. Speaker at Occupational Therapy Summit (Canceled due to COVID-19).
9. Aziz-Zadeh, L. (2019) The brain, the microbiome, and behavior in autism. Help Group Annual Symposium. Los Angeles.
10. Mayer, E.M. (2019) Brain gut microbiome interactions & brain health. NeoTriton Conference. Calgary.
11. Mayer, E. (2020) Gut-Brain connections to behaviors in humans. Microbiome for mars virtual workshop. Online.
12. G. Flores, E. Kilroy, A. Jayashankar, C. Butera, L. Harrison, A. Hossain, A. Nalbach, L. Aziz-Zadeh (2020). Emotion processing in autism spectrum disorder: Potential influence of the gut-brain axis. Diversity, Inclusion & Access (DIA) Jumpstart Research Presentation. Online presentation.
13. Noor, S., Jayashankar, A., & Harrison, L. (2021). Virtual Reality Adaptation of Cyberball paradigm increases Sense of Social Presence and Ostracism. Society of Affective Science (SAS) Annual Conference. (Virtual conference)
14. Jayashankar, A., Harrison, L., Butera, C., Kilroy, E., Kaplan, J., Hossain, A., Nalbach, A., & Aziz-Zadeh, L. (2020). Comparison of AROMA and FIX in motion correction for multiband pediatric clinical neuroimaging. 26th Annual Meeting of the Organization of Human Brain Mapping (OHBM). (Virtual conference)

- **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.

<https://dornsife.usc.edu/labs/cenec>

- **Technologies or techniques**

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

Nothing to report.

- **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.*

Database of MRI, behavioral data, and microbiome data for children with autism and typically developing children. The MRI and behavioral data have been uploaded onto NDAR.

8. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change”.

Name: Lisa Aziz-Zadeh, PhD

Project Role: Principal Investigator

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 1

Contribution to Project: Oversees all aspects of proposed study, including overall recruitment strategy, behavior assessments, research design, data acquisition, oversight of the NDAR data sharing protocol, data analysis, and manuscript preparations.

Name: Emeran Mayer, MD

Project Role: Partnering Principal Investigator (UCLA)

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 1

Contribution to Project: Oversee the bioinformatics and multiomics integration of behavioral, brain and microbiome data. He works closely with Drs. Jacobs and Labus in the planning and interpretation of these analyses, and will be involved in manuscripts resulting from this study.

Name: Jennifer Labus, PhD

Project Role: Co-Investigator (UCLA)

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 1

Contributions to Project: Responsible for cross-correlating the neuroimaging data with microbiome-related data, machine learning analyses, and performing brain-gut-microbiome network analysis in conjunction with Dr. Jacobs. She will also participate in the preparation of manuscripts.

Name: Jonathan Jacobs, MD PhD

Project Role: Co-Investigator (UCLA)

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 1

Contributions to Project: Expertise in the intestinal microbiome and immunology. He will also contribute to the preparation of manuscripts.

Name: Mirella Dapretto, PhD

Project Role: Co-Investigator (UCLA)

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 1

Contributions to Project: Provide clinical and scientific expertise in ASD, brain-imaging studies, and the interpretation of study results.

Name: Sharon O'Neil, PhD

Project Role: Consulting Psychologist

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 1

Contribution to Project: Training in the administration of ADOS and ADI-R and verification of autism diagnosis.

Name: Emily Kilroy, PhD

Project Role: Post-Doctoral Research Associate

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 4

Contribution to Project: Involved in all aspects of the study such as subject recruitment; data acquisition (e.g. behavioral, stool, and brain imaging); data coordination for National Database for Autism Research (NDAR)); administering behavioral assessments and scoring them, stool collection and storage, and cross data analysis (behavioral and microbiota).

Funding: 1 calendar month (of 4) supported by institutional resources.

Name: Aditya Jayashankar

Project Role: Graduate student

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 12

Contribution to Project: Subject recruitment; data acquisition (e.g. behavioral, stool, and brain imaging); administering behavioral assessments and scoring them, stool collection and storage, and cross data analysis (behavioral and microbiota).

Funding: Academic scholarship supported by institutional resources.

Name: Sofronia Ringold

Project Role: Graduate student

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 3

Contribution to Project: Subject recruitment; data acquisition (e.g. behavioral, stool, and brain imaging); administering behavioral assessments and scoring them, stool collection and storage, and cross data analysis (behavioral and microbiota).

Funding: Academic scholarship supported by institutional resources.

Name: Riley McGuire, OTD, OTR/L

Project Role: Occupational Therapy Doctoral Resident

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 9

Contribution to Project: Responsible for administering some of the behavioral assessments, assist with screening participants for participation in the study.

Funding: Academic scholarship supported by institutional resources and fulfillment of doctoral immersion experience

Name: Priten Vora

Project Role: Programmer/Analyst (UCLA)

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 1

Contribution to Project: Perform quality control of all neuroimaging data and will prepare the neuroimaging datasets for analyses.

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

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

New funding for Dr. Mayer:

1. Social Isolation and Discrimination as Stressors Influencing Brain-Gut Microbiome

Alterations Among Filipino and Mexican Americans 05/01/21-12/30/2026

0.30 CM

This proposal aims to examine how the stressors of social isolation and discrimination are related to eating behaviors and dietary patterns, and further, how these behaviors affect the brain-gut-microbiome axis in 300 Mexican and Filipina women because research shows that they encounter a high burden of obesity as well as exposure to social stressors.

Role: Co-I

2. Danone (PI: Gupta)

12/16/2020-03/01/2022

0.60 CM

Pilot study aimed to determine the optimal design for the UCLA/Danone probiotic intervention study related to stress

The goal of this pilot study is to identify the optimal population and methodology for the planned probiotic intervention study in Phase II of the collaboration.

New Funding for Dr. Aziz-Zadeh:

1. Google Faculty Grant. (PI: Aziz-Zadeh)
Language Signals for Belonging Bridging, and Othering
08/24/22 - 08/23/23

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner’s contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner’s facilities for project activities);*
- *Collaboration (e.g., partner’s staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner’s staff use each other’s facilities, work at each other’s site); and*
- *Other.*

Nothing to report.

9. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.*

10. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*