

Award Number: W81XWH-11-1-0774

TITLE: Neural Correlates of Restricted, Repetitive Behaviors in Autism Spectrum Disorders

PRINCIPAL INVESTIGATOR:
Associate Professor of Psychiatry Manoach, Dara

CONTRACTING ORGANIZATION: Massachusetts General Hospital
Boston, Massachusetts 02114-2554

REPORT DATE: October 2013

TYPE OF REPORT: Annual Report

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE October 2013		2. REPORT TYPE Annual		3. DATES COVERED 06 September 2012–05 September 2013	
4. TITLE AND SUBTITLE Neural Correlates of Restricted, Repetitive Behaviors in Autism Spectrum Disorders				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-11-1-0774	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Dara Manoach				5d. PROJECT NUMBER	
E-Mail: dara@nmr.mgh.harvard.edu				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Massachusetts General Hospital Boston, Massachusetts 02114-2554				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT During the period of 09/06/2012-09/05/2013, we enrolled an additional 34 participants with ASD and 10 control participants. Of these, one healthy control and six participants with ASD were unable to complete the study. To date, we were able to acquire phenotyping data, ASD characterization (if applicable), anatomical images, DTI images, fMRI images, and genotyping data for a total of 43 participants with ASD and 24 control participants. Their phenotyping data and ASD characterization have all been updated onto REDCap, a free, secure, web-based application designed to support data capture for research studies. We also reconstructed structural MRI data, unpacked bold and DTI data, performed functional to structural registration, checked registration, performed quality control both during the scanning session and through PACE analysis, ran functional connectivity preprocessing and created seed files for future seed-specific functional connectivity analysis. Due to significant effects of motion on functional and diffusion MRI data, we are taking extra measures to perform quality control on our data including the use of Artifact Detection Tools (ART) on our functional data and DTIPrep on our diffusion data. These tools allow us to automatically and manually remove time-series or gradients that have been affected by motion.					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 5	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
Introduction.....	4
Body.....	4
Key Research Accomplishments.....	4
Reportable Outcomes.....	5
Conclusion.....	5
References.....	5

INTRODUCTION:

The proposed study is the first to utilize state-of-the-art complementary neuroimaging techniques to test the hypothesis that RRBs are associated with specific reductions in brain functional and structural connectivity, and to identify genetic contributions. The primary objective of this study is to illuminate the neural basis of RRBs in ASD and its relation to specific genes. Identification of quantitative trait genetic loci that influence serotonin neurotransmission, mediate connectivity in specific neural circuitry, and are related to RRBs will clarify the pathophysiology of this disabling core feature of ASD and could lead to the use of genomics to individualize pharmacotherapy. Thus, this work will have a direct impact on both research and clinical care.

BODY

Our Statement of Work indicated that during Year 02 of our 3-year study, our goal would be to enroll 14 control participants and 26 participants with ASD who meet our criteria. We would then acquire anatomical, DTI, and fMRI images as well as carry out genotyping on these 40 participants.

During the period of 09/06/2012-09/05/2013, we enrolled an additional 34 participants with ASD and 10 control participants. Of these, one healthy control and four participants with ASD were excluded due to inability to tolerate being in the scanner; one participant with ASD requested to stop the study because the family wanted more data and results than we could provide; and one participant with ASD was excluded because his braces produced artifacts in the MRI data. For the remaining 37, 28 ASD and 9 controls, we were able to acquire phenotyping data, ASD characterization (if applicable), anatomical images, DTI images, fMRI images, and genotyping data. One of these participants was brought back for a second MRI scan because his movements during the first MRI scan brought him out of the scanning protocol's field of view.

Over the past year, in addition to the 44 participants enrolled, we were also in contact with 192 other individuals with ASD. Of these, 71 individuals were not enrolled because with additional screening we found that they didn't meet the inclusion/exclusion criteria, 35 individuals indicated that they were not interested in enrolling in the study, and 36 individuals expressed potential interest but asked us to recontact them again in the future when they are more available or have had their braces taken out. The remaining 49 individuals are still reconsidering the study. We also tried to contact an additional 78 individuals with ASD from the Autism Consortium database but we are still unable to reach them.

For the 67 participants (43 with ASD and 24 controls) who have successfully completed all parts of this study from both Year 01 and 02, phenotyping data have been entered in REDCap, a free, secure, web-based application designed to support data capture for research studies and their saliva samples have been submitted to the Psychiatric & Neurodevelopmental Genetics Unit (PNGU) at MGH for preliminary processing and storage. We have also reconstructed structural MRI data, unpacked bold and DTI data, performed functional and structural registration, and checked their registration. We ran functional connectivity MRI (fcMRI) preprocessing and created seed files for future seed-specific functional connectivity analysis. Preliminary fcMRI analysis confirm that we can localize canonical neural networks (e.g., the default network) in our data, attesting to the integrity of the data and the validity of the analysis techniques.

However, due to the significant effects of motion on functional and diffusion results, we are taking extra measures to perform quality control on our data, both by checking data during the scanning session and through post-hoc qualitative visual checks and quantitative analyses. For the functional data, we are using Dr. Susan Whitfield-Gabrieli's Artifact Detection Tools (ART) for automatic and manual detection of global mean and motion outliers in our fMRI data. ART allows us to remove time-series that have been affected by motion artifacts. For the diffusion data, we are using DTIPrep for automatic and manual removal of diffusion gradients that have been affected by motion, noise/SNR issues, vibrational artifact, venetian blind artifacts, etc. We also quantified both relative and absolute motion (in all translation and rotation directions) of our functional and diffusion data to verify that our ASD and control group do not have significant differences in motion. We are currently working on integrating the data that have gone through ART and DTIPrep into our functional connectivity MRI (fcMRI) and DTI analysis pipelines. For DTI analysis, we will be using Dr. Anastasia Yendiki's TRACULA (TRActs Constrained by Underlying Anatomy) for automatic reconstruction of a set of major white-matter pathways using global probabilistic tractography with anatomical priors.

KEY RESEARCH ACCOMPLISHMENTS

- ✦ Acquired phenotyping data, ASD characterization (if applicable), anatomical images, DTI images, fMRI images, and genotyping data for a total of 43 participants with ASD and 24 control participants
- ✦ All phenotyping data and ASD characterization have been entered into REDCap
- ✦ Reconstructed structural MRI data
- ✦ Unpacked fcMRI and DTI data
- ✦ Performed functional to structural registration. Checked registration.
- ✦ Performed quality control including motion assessment
- ✦ Pre-processed functional connectivity and created seed files for future seed-specific functional connectivity analysis.

REPORTABLE OUTCOMES

This is Year 02 of a 3-year study. There are no reportable outcomes from the data collected by this study yet. From an old data-set collected by our lab, we currently have the following related publication in press:

Peeva M, Tourville JA, Agam Y, Holland B, Manoach DS, Guenther FH. White matter impairment in the speech network of individuals with autism spectrum disorder NeuroImage: Clinical. in press.

CONCLUSION

We have completed data acquisition, entry, quality control, and data pre-processing for a total of 67 subjects, 43 with ASD and 24 controls. Preliminary fcMRI analysis confirm that we can localize canonical neural networks (e.g., the default network) in our data, attesting to the integrity of the data and the validity of the analysis techniques.

Once our dataset is complete, we will test the hypothesis that restrictive, repetitive behaviors (RRBs) are associated with specific reductions in brain functional and structural connectivity, and to identify genetic contributions. The findings will provide a more thorough understanding of the genetic and brain mechanisms that underlie a core and highly disabling feature of ASD, how these differences may influence symptoms such as RRB, and whether specific risk genes may be involved. The findings will also provide pilot data for a larger brain imaging and genetics grant application to NIMH to examine the brain and genetic bases of RRBs. We hope to identify the subset of individuals with ASD whose RRBs would be most likely to benefit from a class of drugs that affect serotonin neurotransmission (SSRIs). Thus, this work will have a direct impact on both research and clinical care.