

AD_____

Award Number: W81XWH-11-1-0774

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

PRINCIPAL INVESTIGATOR:
Dara Manoach

CONTRACTING ORGANIZATION: Massachusetts General Hospital, Boston, MA 02199

REPORT DATE: October 2012

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 2012		2. REPORT TYPE Annual		3. DATES COVERED 06September2011–05September2012	
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, Susan Santangelo E-Mail: dara@nmr.mgh.harvard.edu , ssantangelo@pngu.mgh.harvard.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Massachusetts General Hospital, Boston, MA 02199				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 09/06/2011-09/05/2012, after obtaining MGH IRB approval for this project, we enrolled 17 subjects with ASD and 15 control subjects. Of these, one healthy control and two subjects with ASD were excluded for not meeting IQ inclusion criteria or inability to tolerate being in the scanner. For the remaining 29, we were able to acquire phenotyping data, ASD characterization (if applicable), anatomical images, DTI images, fMRI images, and genotyping data. 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. Hence, data for the 29 subjects who completed the study are now ready for future analysis.					
15. SUBJECT TERMS None provided					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			USAMRMC
			UU	5	19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
Introduction.....	4
Body.....	4
Key Research Accomplishments.....	5
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 01 of our 3-year study, our goal would be to enroll 14 control subjects and 26 subjects with ASD who meet our criteria. We would then acquire anatomical, DTI, and fMRI images as well as carry out genotyping on these 40 subjects.

During the period of 09/06/2011-09/05/2012, after obtaining MGH IRB approval for this project, we enrolled 17 subjects with ASD and 15 control subjects. Of these, one healthy control and two subjects with ASD were excluded for not meeting IQ inclusion criteria or inability to tolerate being in the scanner. For the remaining 29, 15 ASD and 14 controls, we were able to acquire phenotyping data, ASD characterization (if applicable), anatomical images, DTI images, fMRI images, and genotyping data.

We were in contact with 85 individuals with ASD through the Autism Consortium. In addition to the enrolled subjects, 21 subjects expressed potential interest but asked us to recontact them again in the future when they are more available or have reached the age criterion, 56 subjects were not enrolled either because with additional screening we found that they didn't meet the inclusion/exclusion criteria or because they weren't interested in participation.

For 29 subjects who have successfully completed all parts of this study, phenotyping data have been entered in REDCap, a free, secure, web-based application designed to support data capture for research studies. We have also reconstructed structural MRI data, unpacked bold and DTI data, performed functional to structural registration, checked registration, performed quality control both by checking data during the scanning session and through post-hoc analyses, ran functional connectivity MRI (fcMRI) preprocessing and created seed files for future seed-specific functional connectivity analysis. Quality control also excluded the possibility that our use of PACE did not result in artifactual high frequency oscillations. 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. Hence, data for these subjects are ready for future analysis.

For the second year of this project, to increase our sample size and meet our enrollment goals, we are requesting to include younger subjects, lowering the age criterion from 12 to 8. This change has been approved by both the MGH IRB and the Autism Consortium Steering Committee. The rationale for this change is two-fold. Firstly, DTI and structural MRI studies (including Barnea-Goraly et al. 2005) have shown a linear development of white matter in healthy individuals from age 6 through late adolescence/early adulthood. This allows us to statistically control for the effects of age across the range included in our study. In ASD this developmental trajectory is disrupted (Keller et al. 2006), a finding that we aim to replicate and extend to functional connectivity. Our adult head coils are appropriate for ages 8 and up, allowing us to use the same hardware, procedures and analysis for all participants.

Additionally, in order to increase recruitment, we are expanding our recruitment beyond the Autism Consortium. The Neurodevelopmental Disorders Phenotyping Program at the Children's Hospital Boston and the Transcend Lab (Treatment Research and Neuroscience Evaluation of Neurodevelopmental Disorders) at the Martinos Center have both agreed to contact subjects who have participated in their studies in the past and who have agreed to be contacted for future studies. They will inform them of our study and provide our contact information. If subjects are interested in our study, they (or their parent/guardian) will be asked to sign a Release Form allowing us to access their phenotyping data and assessments. We can also recruit subjects with ASD by posting IRB-approved posters online through the Asperger's Association of New England (AANE, <http://www.aane.org>), the Interactive Autism Network (IAN, <http://www.ianproject.org/>), and MGH Aspire (<http://www2.massgeneral.org/youthcare/>). We have also set up recruitment tables at local autism meetings such as the Autism Consortium Symposium.

KEY RESEARCH ACCOMPLISHMENTS

- ✧ Obtained MGH IRB approval for the project
- ✧ Enrolled 17 subjects with ASD and 15 control subjects
- ✧ 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 01 of a 3-year study. There are no reportable outcomes yet.

CONCLUSION

We have completed data acquisition, entry, quality control, and data pre-processing for a total of 29 subjects, 15 with ASD and 14 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. We have expanded our age criteria and our recruitment network and advertising efforts to increase enrollment.

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.

REFERENCES

N. Barnea-Goraly, V. Menon, M. Eckert, L. Tamm, R. Bammer, A. Karchemskiy, C. C. Dant, A. L. Reiss, White matter development during childhood and adolescence: A cross-sectional diffusion tensor imaging study. *Cerebral Cortex* **15**, 1848-1854 (2005).

T. A. Keller, R. K. Kana, M. A. Just, A developmental study of the structural integrity of white matter in autism. *Departmental Neuroscience*. **18:1**, 23-27 (2006).