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14. ABSTRACT

The primary objective of this project is to develop fMRI-based characterizations of functional connectivity networks during natural sleep as a neurologic biomarker for ASD that is suitable for diagnostic use in young children (ages 1-4). Existing neuroimaging and neurobehavioral resources developed by the principal investigators are being mined for ASD-relevant biomarkers. Structural and (constrained) functional meta-analyses of previously published, peer-reviewed neuroimaging studies in ASD have been conducted to inform regions-of-interest for further hierarchical network modeling. We have thus identified (1) consistent regions of brain overgrowth /atrophy and (2) consistent functional activation differences with social behaviors between ASD and typically developing (TD) individuals. These regions-of-interest will be extended through additional functional meta-analyses, network models will be created, and these models will be applied to primary ASD data.

15. SUBJECT TERMS

Autism Spectrum Disorders (ASD); functional magnetic resonance imaging (fMRI); connectivity modeling

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1. INTRODUCTION

Autism spectrum disorders (ASD), characterized by abnormal behavioral patterns and social and communication deficits, are increasing in prevalence and still largely diagnosed behaviorally, an inherently error prone process. Magnetic resonance imaging (MRI) methods are able to detect structural and functional anomalies in patients with ASD; consistent, multi-parametric imaging-based biomarker(s) could lead to earlier and more reliable diagnosis, timely implementation of treatment, and greater overall efficacy of treatment. Through utilization of functional and structural MRI and behavioral data from young subjects, the present proposal seeks to develop imaging biomarkers and characterize associated behaviors to assist clinicians with earlier diagnosis.

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2. KEYWORDS

Autism Spectrum Disorders (ASD); functional magnetic resonance imaging (fMRI); connectivity

3. ACCOMPLISHMENTS

a. What were the major goals of the UTHSCSA site?

This site focused on building a meta-analytic Autism Spectrum Disorders (ASD) model that will be applied to primary data and genetic analyses. Training post-doctoral associates and others to conduct the needed analyses was also needed. Below we outline the major tasks identified in the original Scope of Work (SOW) relevant for this reporting period.

Administrative Tasks (Prior to Aims)

Major Task 1: HRPO approval

Not required.

Major Task 2: Staffing.

The project went through a transition, as regards staffing, recently (see section 5. Changes). As of January 2016, Dr. Fox, the principal investigator, hired, David Neal Brown, a doctoral student in the Clinical Neuro-Psychology program at Fielding Graduate University, to resume analysis of the ASD data. David Brown has extensive clinical experience working with patients with ASD. He is a capable diagnostician and at his practice at the Ecumenical Center he is frequently employed to use his expertise with cases of developmental disorders. He has experience in creating treatment plans and interventions for people with pervasive developmental disorders including ASD. Further, Brown has experience as an educator including special education with conduct disorder youth and as a biology instructor. His academics are strong and broad and he has an excellent background in research as well. Brown was a co-presenter at the 2014 ABCT conference for his project on Nonverbal Learning Disorder as a Neurocognitive Endophenotype for Anxiety in Adults: Implications for CBT Assessment and Intervention. Additionally, he programed the Research Practice Network Database for FGU which required extensive statistical knowledge and understanding of data structure.

Tasks In support of Specific Aim 1: Candidate Biomarker Development (UTHSCSA Site)

Major Task 1 was to develop multi-regional functional-connectivity models of regions involved in ASD using meta- analysis.

Subtask 1: ALE Meta-analysis was to compute anatomical and functional differences between ASD adults and neurotypical controls. These initial meta-analyses were computed in June of 2015, during the last reporting period. We are computing further meta-analyses, which will enable replication and validation analyses with no change to the total original budget, but which will require additional time (see section 5. Changes).

Subtask 2: Single-stage MACM Analysis was to use the output of the structural and functional ALEs as seed regions. We anticipate being able to complete this step by year's end.

Subtask 3: Multi-stage MACM Analyses was to compute Construct graphical (node-and-edge) models using the MACM output. We anticipate that we will begin to compute these models by early 2017.

b. What was accomplished under these goals?

As described in Subtask 1 above, comprehensive meta-analyses are currently being done on existing publications, which include whole-brain imaging data on ASD subjects. Regions are being identified for MACM analysis and will be used to create a predictive model. This model will then be applied to primary subject data.

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

Since his hiring in January 2016, Mr. Brown has received extensive mentorship in MRI theory and application through Dr. Fox's lab. He is currently taking online course in R, Python, and machine learning techniques and recently attended a workshop on novel Path Analysis techniques. Mr. Brown has also received training on structural equation modeling SEM and the use of AMOS and Onyx software packages. He will soon be learning SPM and MatLab.

d. How were the results disseminated to communities of interest?

Nothing to report.

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

By the next reporting period of August 2017 all meta-analysis and ALE processing should be done and MACM results should be producing predictive models for testing.

4. IMPACT

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

Nothing to report.

b. What was the impact on other disciplines?

Nothing to report.

c. What was the impact on technology transfer?

Nothing to report.

d. What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS:

Mariam Ishaque who was hired and began working in March of 2015, subsequently switched the focus of her research in July of 2015. Thereafter, Mariam Ishaque no longer worked on this project. Thus, the project lay relatively dormant until a suitable candidate could be found. To replace Mariam, Dr. Fox (PI) interviewed other candidates for the position. As of January 2016, Dr. Fox hired, David Neal Brown, a doctoral student in the Clinical Neuro-Psychology program at Fielding Graduate University, to resume analysis of the ASD data. Since coming on to the project Mr. Brown has begun to conduct further meta-analyses to replicate previous findings and will continue work in support of Subtask 2 and 3 of Aim 1.

No scientific, design or experiment problems have occurred here. We completed the initial meta-analyses exploring anatomical and functional differences between ASD adults and neurotypical controls, as planned. After further meta-analyses described above in Subtask 1, we will be prepared for the next stages of the project.

As described in detail above, we have encountered problems in finding a qualified candidate who has expertise in fMRI statistical analyses and autism. We solved this problem as described above, by hiring and training a graduate student, David Brown, to provide assistance under the supervision of Dr. Fox (PI). Therefore, unexpended funds from the previous year's budget will be carried forward to the coming year to support new staff and further the project's goals.

6. PRODUCTS:

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. What individuals have worked on the project?

Work on this project at UTHSCSA has been limited to the following individuals:

Peter T Fox, MD (dedicated at 5% effort) is the Principal Investigator (PI) (ORCID ID: 0000-0002-0465-2028) on this project. Dr. Fox is a neuroimaging researcher and neurologist at the University of Texas Health Science Center at San Antonio. He is a professor in the Department of Radiology with joint appointments in Radiology, Medicine, and Psychiatry and is the founding director of the Research Imaging Institute (RII), a department-level, research-dedicated component of the University of Texas Health Science Center at San Antonio. He has vast experience in fMRI methodology and has published extensively in neuroimaging research. Currently, Dr. Fox specializes in Nuclear Medicine and Diagnostic Neuroimaging, having over 37 years experience in the field.

Mariam Ishaque (dedicated at 50% effort) is a pre-doctoral student, enrolled in the dual degree M.D./ Ph.D. Biomedical Sciences program at UTHSCSA. Under the supervision of Dr. Fox, she has conducted functional and structural meta-analyses in support of Aim 1 (Major Task 1/Subtask 1), the results of which will be used further in modeling and analyses.

David Brown (dedicated at 50% effort) is a doctoral student in the Clinical Neuro-Psychology program at Fielding Graduate University. Under the supervision of Dr. Fox, he is continuing meta-analysis of the ASD data and will be using the structural and functional ALEs to seed a MACM analysis in support of Aim 1 (Major Task 1/ Subtasks 2 and 3).

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

Nothing to report.

c. What other organizations were involved as partners?

As per the original application, the other organizations involved as partners are Yale University (Dr. Glahn, P.I. at that site) and the University of California San Diego site (Dr. Courchesne, P.I. at that site).

8. SPECIAL REPORTING REQUIREMENTS

a. COLLABORATIVE AWARD:

This project is part of a Collaborative Award and this Progress Report is from the University of Texas Health Science Center San Antonio site (Fox, the overall project P.I.). Comparable progress reports from Dr. Glahn at Yale University and Dr. Eric Courchesne at University of California San Diego will be submitted separately.

9. APPENDICES:

See REFERENCES, below:

REFERENCES

1. Nickl-Jockschat T, Habel U, Michel TM, Manning J, Laird AR, Fox PT, Schneider F, Eickhoff SB. 2012. Brain structure anomalies in autism spectrum disorder--a meta-analysis of VBM studies using anatomic likelihood estimation. Hum Brain Mapp 33(6): 1470-89.
2. Philip RC, Dauvermann MR, Whalley HC, Baynham K, Lawrie SM, Stanfield AC. 2012. A systematic review and meta-analysis of the fMRI investigation of autism spectrum disorders. Neurosci Biobehav Rev 36(2): 901-42.