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TITLE: Resting State Functional MRI to Find the Correct Surgical Target to Stop Seizures in Tuberous Sclerosis Complex

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14. ABSTRACT
Tuberous sclerosis complex (TSC) occurs in 1/5800 live births, with a 1/20,000 population prevalence. Notably TSC patients experience severe morbidity: 90% have epilepsy, 55% have intellectual disability (ID), 20-50% have autism spectrum disorder (ASD), and 55% have neuropsychological deficits. Surgery leads to cure of epilepsy in 56% of patients with tuberous sclerosis complex (TSC). The number one factor in cure is correctly locating the area causing the seizures and then surgically destroying it. Thus far, three meta-analyses show technological advances in localization and surgical technique have not budged the 56% cure rate. Only one measure has produced results above current technology, resting state functional MRI (RS) whole-brain analysis. The following research has the goal of improving the surgical planning and outcomes for patients with TSC as well as identifying RS intrinsic functional connectivity (iFC) networks associated with comorbidities (i.e. autism spectrum disorder, language impairment, social cognition impairment, and intellectual disability. This multi-site investigation will utilize data from retrospective medical record chart review and prospective standard of care procedures within pediatric TSC patient populations at 3 study sites. At this time, study efforts have focused on regulatory, retrospective case identification and data extraction, prospective case enrollment, and data analysis pipeline development. There are not results to report at this time.

15. SUBJECT TERMS
Resting state functional MRI, tuberous sclerosis complex, epilepsy, autism spectrum disorder, language impairment, social cognitive impairment, intellectual disability, pediatric

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TABLE OF CONTENTS

1. INTRODUCTION:

Tuberous sclerosis complex (TSC) occurs in 1/5800 live births, with a 1/20,000 population prevalence. Notably TSC patients experience severe morbidity: 90% have epilepsy, 55% have intellectual disability (ID), 20-50% have autism spectrum disorder (ASD), and 55% have neuropsychological deficits. Surgery leads to cure of epilepsy in 56% of patients with tuberous sclerosis complex (TSC). The number one factor in cure is correctly locating the area causing the seizures and then surgically destroying it. Thus far, three meta-analyses show technological advances in localization and surgical technique have not budged the 56% cure rate. Only one measure has produced results above current technology, resting state functional MRI (RS) whole-brain analysis. In the broad epilepsy population, including those with TSC, RS locates the area of the brain generating seizures with 93% sensitivity and 75% accuracy. The following research has the goal of improving the surgical planning and outcomes for patients with TSC as well as identifying RS intrinsic functional connectivity (iFC) networks associated with comorbidities (i.e. autism spectrum disorder, language impairment, social cognition impairment, and intellectual disability. This multi-site investigation will utilize data from retrospective medical record chart review and prospective standard of care procedures within pediatric TSC patient populations from Phoenix Children's Hospital (PCH), Texas Children's Hospital (TCS), and Cincinnati Children's Hospital Medical Center (CCHMC).

2. KEYWORDS:

Resting state functional MRI, tuberous sclerosis complex, epilepsy, autism spectrum disorder, language impairment, social cognitive impairment, intellectual disability, pediatric

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: To assess the effect of preoperative resting state functional MRI (RS)-guidance in TSC. RS-guidance impact on surgical planning, and seizure outcomes in TSC is unknown. Additionally, the accuracy of RS seizure onset zone (SOZ) as the true area of seizure generation in TSC may best be evaluated in conjunction with RS SOZ destruction and seizure outcomes in TSC.	**Timeline (Months)**	**Site 1 (PCH)**	**Site 2 (CCHMC)**	**Site 3 (TCH)**
***Milestone 1**: IRB review and approval of study protocols.*	1-3	100% PCH: 08/05/20	95% 04/27/2021	65% Pending
Major Task 1: To assess the effect of preoperative RS-guided evaluation on surgical planning.	4-22	Y1Q4 Goal: 2 Total Goal: 40	Y1Q4 Goal: 1 Total Goal: 10	Y1Q4 Goal: 1 Total Goal: 10
Subtask 1.1: Patient enrollment - Study subjects will include 60 with prospective RS studies used to guide epilepsy surgery	4-22	**10%** Y1Q4 Enrolled: 2/8 Total Enrolled: 4/40	**0%** Y1Q4 Enrolled: 0/1 Total Enrolled: 0/10 Started enrolling 09/2021	**0%*** Y1Q4 Enrolled: 0/1 Total Enrolled: 0/10 *Pending IRB/HRPO approvals, not enrolling
Subtask 1.2: Surgery planning. Surgery conference with all relevant patient information and test results, except for the RS.RS data presented and changes to surgical plan noted, determinations to proceeding to surgery, surgical approach, surgical target, and changes in further testing.	4-22	**7.5%** Y1Q4 Enrolled: 1/8 Total Enrolled: 3/40	**0%**	**0%**
Major Task 2: To assess the effect of preoperative RS-guided evaluation on Engel 1 outcome rate at 1 year in pediatric TSC.	23-25	Y1Q4 Goal: N/A Total Goal: 220	N/A	N/A
Subtask 2.1: Summarize and compare baseline demographic and clinical factors between subjects with and without RS-guided surgery. Study subjects will include 110 with RS studies used to guide epilepsy surgery and 110 controls with surgery determined without RS guidance.	23-25	**9.1%** Identified: 20/220	-	-
Major Task 3: To assess the association between destruction/disconnection of the RS seizure onset zone (SOZ) and Engel 1 outcome rate in pediatric TSC. While pre-surgery RS evaluation identifies SOZ, this may not be destroyed (or disconnected) during surgery for safety.	10-28	Y1Q4 Goal: N/A Total Goal: ≈ 112	N/A	N/A

Subtask 3.1: Pre-operative RS SOZ will be co-registered to the post-operative structural MRI for determination of extent of the destruction/disconnection of the RS SOZ.	10-28	**9.8%** Identified: 9/112	-	-
Subtask 3.2: Two blinded epilepsy team doctors will view the area and determine if all, partial, or none of the RS SOZ was destroyed. Differences in determinations will be discussed between the reviewers and if needed a third epilepsy team doctor will make the final determination.	10-30	-	-	-
Specific Aim 2: To assess the intrinsic functional networks that sub-serve language capacity, social cognition, and intelligence in TSC.	**Timeline (Months)**	**Site 1 (PCH)**	**Site 2 (TCH)**	**Site 3 (CCHMC)**
Major Task 4: To assess the association of the pure-language network intrinsic functional connectivity (iFC) with language capacity.	22-36	Y1Q4 Goal: N/A Total Goal: ≈ 137	N/A	N/A
Subtask 4.1: ASD and language impairment will be determined by preoperative testing. Language disability and social interaction functions will have been assessed in all patients with ASD. Blinded review by 2 experts will assess the iFC of the STG, STS, and IFG to establish hemispheric dominance by greater spatial coverage and classify iFC as normal/abnormal according to published guidelines; 137 subjects' data will be used	22-36	**1.5%** Identified: 2/137	-	-
Milestone 2: *HRPO approval received*	1-3	100% HRPO: 10/10/20	100% 08/23/2021	0% TBD
Major Task 5: To assess the association of social cognitive network iFC with symptoms of ASD.	22-36	Y1Q4 Goal: 0 Total Goal: ≈ 137	N/A	N/A
Subtask 5.1: ASD will be determined by preoperative testing; 137 subjects' data will be used.	4-22	**2.9%** Identified:4/137	-	-
Subtask 5.2: Assess the iFC of the STG, STS, and IFG to establish hemispheric dominance by greater spatial coverage and classify iFC of the non-dominant MFG and bilateral precuneus as normal/abnormal according to published guidelines.	22-36	-	-	-
Subtask 5.3: Generate a social cognitive network iFC.	22-36	-	-	-
Major Task 6: Assess the association of abnormal connectivity pattern associated with ID, in pediatric TSC.	22-36	Y1Q4 Goal: 0 Total Goal: ≈ 122	N/A	N/A
Subtask 6.1: Blinded review by 2 experts will assess the presence of the long-range fronto-parietal network.	22-36	-	-	-
Subtask 6.2: IQ will be determined by preoperative testing; Data from 122 patients with preoperative RS and available IQ measure.	4-22	**5.7%** Identified: 7/122	-	-
Milestone 3*: Manuscript on use of the imaging in pre-clinical studies.*	18-24	-	-	-

Prospective	Year 1				Year 2				Year 3				Total
Target Enrollment (per quarter)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	
Site 1 (PCH)	-	2	6	8	8	8	8	-	-	-	-	-	40
Site 2 (TCH)	-	1	1	2	2	2	2	-	-	-	-	-	10
Site 3 (CCHMC)	-	1	1	2	2	2	2	-	-	-	-	-	10
Target Enrollment (cumulative)	**-**	**4**	**8**	**12**	**12**	**12**	**12**	**-**	**-**	**-**	**-**	**-**	**60**

What was accomplished under these goals?

Year 1, (08/15/2020 – 08/14/2021); Months 1-12

Major Activities: Y1 activities focused on initial regulatory tasks, validation of analysis pipeline, prospective patient enrollment, and identification/data entry of retrospective cases:

(a) PCH, TCH/BCM, and CCHMC local IRB "Request to Rely" applications
(b) Submission/Approval of the study protocol, master consent forms to PCH IRB / SMART IRB / HRPO
(c) SMART IRB Reliance Agreements
(d) Submission/Approval of site-questionnaires for TCH/BCM and CCHMC to PCH IRB
(e) Submission/Approval of site-specific documents TCH/BCM and CCHMC to PCH IRB
(f) HRPO submission packet and Site-Specific Addendum Forms for TCH/BCM and CCHMC
(g) Prospective enrollment (PCH).
(h) Retrospective case identification, data entry
(i) Analysis pipeline validation (PCH)

Specific Objectives: Y1 objectives included:

(a) Milestone 1 – Local IRB/SMART and PCH IRB review/approval of protocol/site materials.
(b) Milestone 2 – HRPO review/approval of PCH IRB approved protocol/site materials.
(c) Subtask 1.1 – Prospective: (+) pre-surgical rs-fMRI (RS), (+) pre-surgical conference
(d) Subtask 2.1 – Retro/Prospective: (+/-) pre-surgical RS, (+) 1-year Engel score
(e) Subtask 3.1 – Retro/Prospective: (+/-) destruction of RS SOZ, (+) 1-year Engel score
(f) Subtask 4.1 – Retro/Prospective: (+) RS, (+) Language assessment
(g) Subtask 5.1 – Retro/Prospective: (+) RS, (+) ASD assessment
(h) Subtask 6.2 – Retro/Prospective: (+) RS, (+) IQ assessment

Significant Results and Key Outcomes:

(a) Milestone 1: Local, SMART, PCH IRB approvals
- TCH/BCM (75%):
  - Local IRB approval (100%)
  - SMART IRB approval (100%)
  - PCH IRB approval (25%, Q4 site-questionnaire submitted)
- CCHMC (100%):
  - Local IRB approval (100%)
  - SMART IRB approval (100%)
  - PCH IRB site approval (100%), Y1 Continuing Review (100%)
- PCH (100%):
  - Local IRB approval (100%)
  - SMART IRB approval (100%)
  - PCH IRB site approval (100%), Y1 Continuing Review (100%)

(b) Milestone 2: HRPO approvals
- TCH/BCM (0%)
- CCHMC (100%) – Site-specific documents, Y1 Continuing Review
- PCH (100%) - Site-specific documents, Y1 Continuing Review

(c) Subtask 1.1 – Cases Identified: PCH 6/40 (15%); PCH Enrolled: 4/40 (10%)
(d) Subtask 2.1 – Cases Identified: PCH 20/220 (9.1%)
(e) Subtask 3.1 – Cases Identified: PCH 11/112 (9.8%)
(f) Subtask 4.1 – Cases Identified: PCH 2/137 (1.5%)
(g) Subtask 5.1 – Cases Identified: PCH 4/137 (2.9%)
(h) Subtask 6.2 – Cases Identified: PCH 7/122 (5.7%)

Other Achievements:

(a) Biweekly multi-site communication with key study personnel.
(b) Subtask 3.1-6.2 – preliminary analysis/pipeline development.

Goals Not Met:

(a) Milestone 1 & 2:
- TCH/BCM: PCH IRB approvals, HRPO review/approval (expected Y2Q1)

(b) Subtask 1.1:
- PCH: Open to Enroll, Enrolled 4/16 patients
- TCH/BCM: Not Open to Enroll, Enrolled 0/4 patients.
- CCHMC: Open to Enroll, Enrolled 0/1 patients.

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

Training: training activities included online SMART IRB courses, one-on-one work with a PI/senior post-doc for RS preprocessing and analysis pipeline development.

Professional development: presentation of study aims during grand rounds and epilepsy case conferences, individual study or analysis methods and study population via completion of online analysis tutorials and review of existing literature.

How were the results disseminated to communities of interest?

Nothing to report. Manuscript in preparation for initial analysis pipeline development with data from retrospective and control subject data.

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

During Y2Q1 we will:

- Complete outstanding IRB/HRPO approval procedures for TCH/BCM.
- Continue retrospective/prospective source data collection at PCH.
- Control data preprocessing.
- Continue prospective enrollment at PCH, CCHMC, and TCH/BMC (upon approval).

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?

Nothing to Report.

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:

Changes in approach and reasons for change:

Nothing to Report.

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

Delay 1: External site local IRB, SMART IRB (SMART IRB), HRPO approvals process.
Corrective Actions: Ongoing discussion/support for Local/SMART IRB approval process with external sites. Complied with the local IRB “Request to Rely” process prior to the SMART IRB approval. Updated site-specific materials to meet local IRB contextual review revision requests for PCH IRB submissions. Updated HRPO submission packet pending IRB approvals.
Outcome: Local, SMART IRB, and PCH IRB process completed for PCH CCHMC, TCH/BCM pending Y2Q1 approval.

Delay 2: External site staff turnover, vacation, and leave of absence.
Corrective Actions: Updated new staff on project status, created PCH IRB profiles, update SMART IRB POC.
Outcome: Updated contacts and POCs for all sites, updated DOA logs.

Delay 3: Limited number of prospective cases, low enrollment/delayed site opening.
Corrective Actions: Ongoing discussion and education on study aims, requirements, and inclusion/exclusion criteria with referring physicians. CCHMC now open to enrollment with future patients identified.
Outcome: Identified potential patients and coordinated outreach and consenting opportunities at future appointments.

Changes that had a significant impact on expenditures

The delays in IRB/HRPO approval of the secondary site (CCHMC and TCH/BCM) resulted in delayed prospective requirement. Thus, the sites did not invoice the study for participant related costs. This impacted the Y1 expenditures (lower enrollment, fewer expenses) and will impact the Y2 expenditures (greater enrollment, great expenses).

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

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.

6. PRODUCTS:
Publications, conference papers, and presentations

Journal publications.

Nothing to Report.

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers and presentations.

Grand Rounds Presentation: (06/21/2021)
Venue: Pediatric Neuroscience Grand Rounds (Virtual), The University of Arizona College of Medicine – Tucson; Title: *Innovations in Rs-fMRI in Pediatric Neuroscience*

Website(s) or other Internet site(s)

Nothing to Report.

Technologies or techniques

Nothing to Report.

Inventions, patent applications, and/or licenses

Nothing to Report.

Other Products

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Varina Boerwinkle, MD
Project Role:	Lead/Site PI (PCH)
Researcher Identifier (ORCID / eRA Com):	0000-0002-1429-2994 / VBOERWINKLE
Nearest person month worked:	2.9
Contribution to Project:	Protocol modification; regulatory document revision feedback and signoff; offsite PI/personnel biweekly communications; retrospective dataset and preliminary pipeline feedback

Name:	Sarah Wyckoff, PhD
Project Role:	Clinical Research Coordinator / Research Scientist II (PCH)
Researcher Identifier (ORCID / eRA Com):	0000-0002-0587-1185 / WYCKOFF
Nearest person month worked:	6
Contribution to Project:	Protocol and regulatory document preparation; IRB/SMART IRB submission/revisions/agreements; offsite personnel biweekly communications; Prospective patient screening/consent; Retrospective Case Identification; Data Entry; preliminary analysis pipeline development

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.

What other organizations were involved as partners?

Organization Name:	Texas Children's Hospital / Baylor College of Medicine
Location of Organization:	6701 Fannin St, Suite 1230.01 Houston, TX 77030
Contribution to the project:	Facilities (e.g., partner's staff use the facilities/patients for project activities) Collaboration (e.g., partner's staff work with project staff on the project)

Organization Name:	Cincinnati Children's Hospital
Location of Organization:	3333 Burnet Ave Cincinnati, OH 45229-3039
Contribution to the project:	Facilities (e.g., partner's staff use the facilities/patients for project activities) Collaboration (e.g., partner's staff work with project staff on the project)

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS

N/A

QUAD CHARTS:

Attached.

9. APPENDICES:

N/A