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

PRINCIPAL INVESTIGATOR: Varina L. Boerwinkle, MD

CONTRACTING ORGANIZATION: Phoenix Children's Hospital, Phoenix, AZ

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Varina L. Boerwinkle, MD vboerwinkle@phoenixchildrens.com
Sarah N. Wyckoff, PhD swyckoff@phoenixchildrens.com

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Phoenix Children's Hospital
1919 E Thomas Rd
Phoenix, AZ 85016-7710

Texas Children's Hospital /
Baylor College of Medicine
6701 Fannin St,
Suite 1230.01
Houston, TX 77030

Cincinnati Children's Hospital
3333 Burnet Ave
Cincinnati, OH 45229-3039

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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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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, previous primary site)**	**Site 2 (CCHMC)**	**Site 3 (TCH)**	**Site 4 (UNC, new primary site)**
***Milestone 1**: IRB review and approval of study protocols.*	1-3	100% 08/05/20	100% 04/27/2021 05/24/2021	100% 10/15/2021	100% 06/2022
Major Task 1: To assess the effect of preoperative RS-guided evaluation on surgical planning.	4-22	Y2Q4 Goal: 0 Total Goal: 10	Y2Q4 Goal: 0 Total Goal: 10	Y2Q4 Goal: 0 Total Goal: 40	Y2Q4 Goal: 0 Total Goal: 6
Subtask 1.1: Patient enrollment - Study subjects will include 60 with prospective RS studies used to guide epilepsy surgery	4-22	**40%** Y2Q4 Enrolled: 0/0 Total Enrolled: 4/10	**40%** Y2Q4 Enrolled: 0/0 Total Enrolled: 4/10	**0%** Y2Q4 Enrolled: 0/0 Total Enrolled: 0/40	**0%** Y2Q4 Enrolled: 0/0 Total Enrolled: 0/6
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	**20%** Y2Q4 Enrolled: 0/0 Total Enrolled: 4/10 Total Assessed: 2/4	**30%** Y2Q4 Enrolled: 0/0 Total Enrolled: 4/10 Total Assessed: 3/4	**0%*** Y2Q4 Enrolled: 0/0 Total Enrolled: 0/40	**0%*** Y2Q4 Enrolled: 0/0 Total Enrolled: 0/6
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	Total Goal: 220	N/A	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	**18.18%** Identified: 40/220	-	-	-
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	Total Goal: ≈ 112	N/A	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)**	**Site 4 (UNC, new primary site)**
Major Task 4: To assess the association of the pure-language network intrinsic functional connectivity (iFC) with language capacity.	22-36	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	**13.87%** Identified: 19/137	-	-	
Milestone 2: *HRPO approval received*	1-3	100% 10/10/20	100% 08/23/2021	0% 11/15/2021	0%
Major Task 5: To assess the association of social cognitive network iFC with symptoms of ASD.	22-36	Total Goal: ≈ 137	N/A	N/A	N/A
Subtask 5.1: ASD will be determined by preoperative testing; 137 subjects' data will be used.	4-22	**17.52%** Identified:24/137	-	-	-
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	Total Goal: ≈ 122	N/A	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	**17.21%** Identified: 21/122	-	-	-
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 2, (08/15/2021 – 08/14/2022); Months 12-24
Major Activities:

Y2Q3-Q4 activities focused on transferring the grant from PCH to UNC, ongoing regulatory tasks, and identification/data entry/analysis of retrospective/prospective cases:
(a) Prospective screening/enrollment: PCH, CCHMC
(b) Data analysis: CCHMC data transfer, rs-fMRI analysis/case presentation and documentation
(c) Retrospective case identification, data entry, de-identification
(d) UNC began grant transfer process: Submitted protocol to UNC IRB 5/3/2022, Approved 06/2022
(e) Project meeting with all sites to coordinate grant transfer, consent form rebranding, and local/SMART IRB reliance agreements process
(f) Submit Data Transfer Agreement to PCH legal to authorize de-identified data transfer to UNC

Y2Q2 activities focused on outstanding regulatory tasks, prospective patient enrollment, and identification/data entry/analysis of retrospective cases:
(a) TCH/BCM site/materials applications HRPO (approved 11/15/2021)
(b) Prospective screening/enrollment: PCH, CCHMC
(c) Data analysis: CCHMC data transfer, rs-fMRI analysis/case presentation and documentation
(d) Retrospective case identification, data entry

Y2Q1 activities focused on outstanding regulatory tasks, prospective patient enrollment, and identification/data entry/analysis of retrospective cases:
(a) TCH/BCM site/materials applications, PCH IRB and HRPO
(b) CCHMC site/materials application, HRPO
(c) PCH protocol modification application, PCH IRB and HRPO
(d) Prospective enrollment: PCH, CCHMC
(e) Retrospective case identification, data entry

Specific Objectives:
Y2Q3-Q4 objectives included:
(a) Milestone 1 – IRB
(b) Milestone 2 – HRPO
(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

Y2Q2 objectives included:
(a) Milestone 1 – N/A
(b) Milestone 2 – HRPO review/approval of BCM/TCH addendum and PCH modification
(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

Y2Q1 objectives included:
(a) Milestone 1 – PCH IRB review/approval of PCH modification and TCH/BCM site materials.
(b) Milestone 2 – HRPO review/approval of CCHMC and TCH/BCM site materials, PCH modification
(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:

Y2Q3-Q4:

(a) Milestone 1 – UNC local IRB resubmission to initiate grant transfer (5/3/2022)
(b) Milestone 2 – HRPO initial site packet for UNC materials in preparation
(c) Subtask 1.1 – Cases Enrolled: 1/10, data analyzed, surgical conference documented
(d) Subtask 2.1 – Cases Identified: PCH 20/220 (9.1%), data abstracted, de-identification
(e) Subtask 3.1 – Cases Identified: PCH 11/112 (9.8%), data abstracted, de-identification
(f) Subtask 4.1 – Cases Identified: PCH 2/137 (1.5%), data abstracted, de-identification
(g) Subtask 5.1 – Cases Identified: PCH 2/137 (1.5%), data abstracted, de-identification
(h) Subtask 6.2 – Cases Identified: PCH 5/122 (4.1%), data abstracted, de-identification

Y2Q2:

(a) Milestone 1: N/A
(b) Milestone 2: HRPO approvals
    - TCH/BCM Site-Specific Addendum Form (approved – 11/15/2021)
(c) Subtask 1.1 – Cases Enrolled: 1/10, data analyzed, surgical conference documented
(d) Subtask 2.1 – Cases Identified: PCH 20/220 (9.1%), data abstracted
(e) Subtask 3.1 – Cases Identified: PCH 11/112 (9.8%), data abstracted
(f) Subtask 4.1 – Cases Identified: PCH 2/137 (1.5%), data abstracted
(g) Subtask 5.1 – Cases Identified: PCH 2/137 (1.5%), data abstracted
(h) Subtask 6.2 – Cases Identified: PCH 5/122 (4.1%), data abstracted

Y2Q1:

(a) Milestone 1: IRB approvals
    - TCH/BCM: PCH IRB (10/15/2021) approved site/materials
    - PCH: PCH IRB (11/4/20201) approved protocol modification v2
(b) Milestone 2: HRPO approvals
    - CCHMC Site-Specific Addendum Form (approved - 8/23/2021)
    - TCH/BCM Site-Specific Addendum Form (submitted)
    - PCH Site-Specific Addendum Form (submitted)

(c) Subtask 1.1 – Cases Identified: PCH 6/10 (%); PCH Enrolled: 2/10 (%)
(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 2/137 (1.5%)
(h) Subtask 6.2 – Cases Identified: PCH 5/122 (4.1%)

Other Achievements:

(a) Biweekly multi-site communication with key study personnel.
(b) Prepared Data Transfer Agreement for PCH legal submission.
(c) Completed REDCap study project for data entry and secure transfer to UNC

Goals Not Met:

(a) Subtask 1.1:
    - PCH: enroll 4/24 patients.
    - TCH/BCM: enroll 0/6 patients.
    - CCHMC: enroll 4/6 patients.
    - Complete transfer of grant from PCH to UNC.

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 Y3Q1 we will:

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

4. IMPACT:

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.
Desired Outcome: Local, SMART IRB, and UNC IRB process completed/in-process for CCHMC, TCH/BCM, UNC Y3Q1.

Delay 2: Closure of PCH primary site and PI/grant transfer to UNC.
Corrective Actions: Updated new staff on project status, created UNC IRB profiles, update SMART IRB POC.
Outcome: Updated contacts and POCs for all sites, updated DOA logs.

Changes that had a significant impact on expenditures

Closure of PCH primary site and PI/grant transfer to UNC. All recruitment and enrollment suspended at this time.

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.

2022 Cincinnati Children's Hospital Neurology Grand Rounds, “Clinical Evidence Based fMRI in Modern Neurology Practice Today and What is on the Horizon” Jan 5

2021 UCSF Grand Rounds Autumn Ivy Research Spotlight, “Clinical and Translational Research Applications of Resting State Functional MRI, Nov 15

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:	1.8
Contribution to Project:	Project coordination; Protocol modification; regulatory document revision feedback and signoff; offsite PI/personnel biweekly communications; retrospective dataset and preliminary pipeline feedback; data analysis/interpretation/presentation, Surgical case review documentation.
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:	5.8
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; Data transfer; Surgical case review documentation

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

Yes, PCH is no longer the grant recipient. PI and Grant have been transferred to UNC.

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)
Organization Name:	University of North Carolina – Chapel Hill
Location of Organization:	170 Manning Dr, CB# 7025 Chapel Hill, NC 27599-7025
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