Sample Application for Small Business Funding

Through the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs, NIA aims to help small businesses develop effective treatments and interventions for healthy aging. NIH small business funding is competitive, and resubmissions are a common and important part of the award process.

Find more NIA sample applications and information about SBIR/STTR funding:
https://www.nia.nih.gov/research/sbir/nia-small-business-sample-applications

PI: **Wighton, Paul**	Title: Unbiased longitudinal neuromorphometry for clinical decision support	
Received: 09/04/2018	FOA: PAS18-188 Clinical Trial:Optional	Council: 01/2019
Competition ID: FORMS-E	FOA Title: Advancing Research on Alzheimer's Disease (AD) and Alzheimer's-Disease-Related Dementias (ADRD) (R41/R42 Clinical Trial Optional)	
1 R42 AG062026-01A1	Dual:	Accession Number: 4209265
IPF: 10032164	Organization: CORTICOMETRICS, LLC	
Former Number:	Department:	
IRG/SRG: ZRG1 SBIB-T (10)B	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: [redacted] Year 2: [redacted] Year 3: [redacted]	Animals: N Humans: N Clinical Trial: N Current HS Code: 10 HESC: N	New Investigator: Early Stage Investigator:
Senior/Key Personnel:	*Organization:*	*Role Category:*
Paul Wighton	CORTICOMETRICS, LLC	PD/PI
Bruce Fischl	Massachusetts General Hospital (The General Hospital Corp)	MPI
STEVEN ARNOLD	MASSACHUSETTS GENERAL HOSPITAL	Co-Investigator
Otto Rapalino	Massachusetts General Hospital (The General Hospital Corp)	Co-Investigator
Brian Edlow	Massachusetts General Hospital (The General Hospital Corp)	Co-Investigator
Martin Reuter	Massachusetts General Hospital (The General Hospital Corp)	Co-Investigator
STEVEN STUFFLEBEAM	Massachusetts General Hospital (The General Hospital Corp)	Co-Investigator
Nicholas Schmansky	CORTICOMETRICS, LLC	Other Professional-CEO, Software Engineer

OMB Number: 4040-0001
Expiration Date: 10/31/2019

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier
AG062026

b. Agency Routing Number

2. DATE SUBMITTED
2018-09-04

Application Identifier
Longitudinal_FT

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION

Organizational DUNS*: [redacted]

Legal Name*: CORTICOMETRICS, LLC
Department:
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*:
Province:
Country*:
ZIP / Postal Code*:

Person to be contacted on matters involving this application
Prefix: First Name*: Nick Middle Name: Last Name*: Schmansky Suffix:
Position/Title:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*:
Province:
Country*:
ZIP / Postal Code*:
Phone Number*: [redacted] Fax Number: Email: [redacted]

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** [redacted]

7. TYPE OF APPLICANT* R: Small Business

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

❍ New ● Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Unbiased longitudinal neuromorphometry for clinical decision support

12. PROPOSED PROJECT
Start Date* Ending Date*
05/01/2019 04/30/2022

13. CONGRESSIONAL DISTRICTS OF APPLICANT
[redacted]

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Paul Middle Name: Last Name*: Wighton Suffix:
Position/Title: Staff Scientist
Organization Name*: CORTICOMETRICS, LLC
Department:
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*:
Phone Number*: [redacted] Fax Number: Email*: [redacted]

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested* [redacted]
b. Total Non-Federal Funds* [redacted]
c. Total Federal & Non-Federal Funds* [redacted]
d. Estimated Program Income* [redacted]

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:
b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Nick Middle Name: Last Name*: Schmansky Suffix:
Position/Title*: Co-Founder, CEO
Organization Name*: CorticoMetrics LLC
Department:
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*:
Phone Number*: [redacted] Fax Number: Email*: [redacted]

Signature of Authorized Representative*
Nicholas Schmansky

Date Signed*
09/04/2018

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 03/31/2020

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ○ Yes ● No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

○ Yes ○ No

If "No" to AVMA guidelines, describe method and provide scientific justification

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

Tracking Number: GRANT12703690

Funding Opportunity Number: PAS-18-188 . Received Date: 2018-09-04T15:35:50.000-04:00

PHS 398 Cover Page Supplement

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ○ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

❑ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ○ Yes ● No

If the answer is "Yes" then please answer the following:

*Previously Reported: ○ Yes ○ No

5. Change of Investigator/Change of Institution Section

❑ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

Tracking Number: GRANT12703690 Funding Opportunity Number: PAS-18-188 . Received Date: 2018-09-04T15:35:50.000-04:00

Project Summary

Normal human neuroanatomy is incredibly variable, and increases with age. This impedes the ability of neuroimaging to detect effects in neurological conditions such as Alzheimer's disease (AD), Huntington's disease (HD), multiple sclerosis (MS) and schizophrenia. Most of the recently available state-of-the-art quantitative imaging tools still use cross-sectional methods to analyze repeated scans. These tools lack the sensitivity to monitor subtle progressive changes because such approaches do not account for the large intrinsic variability of normal neuroanatomy. The goal of this project is to commercialize a longitudinal, neuro-morphometric image processing pipeline for use in radiology, neurology and related clinical fields. The successful completion of this project will result in a clinically useful neuro-morphometric longitudinal analysis stream with more statistical power than is currently available commercially. This increase in power will directly translate into an enhanced ability to detect and assess progression at both the individual and group levels. It will also alleviate a major pain point in current longitudinal neuroradiology reading workflows, reducing radiology report turnaround times (RTAT).

Project Narrative

The proposed project will develop software to help clinicians quantitatively assess and interpret changes in brain MRI data in a way that integrates seamlessly into an existing clinical workflow. It will help radiologists detect changes to brain structures earlier and more accurately, in neurological conditions such as Alzheimer's disease (AD), Huntington's disease (HD), multiple sclerosis (MS) and schizophrenia. The resulting efforts will translate into an enhanced ability to detect and assess disease progression, and reduce radiology report turnaround time.

BIOGRAPHICAL SKETCH

NAME: Wighton, Paul

eRA COMMONS USER NAME (agency login): [redacted]

POSITION TITLE: Staff Scientist, CorticoMetrics LLC

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
University of Guelph, Guelph, Ontario	BSc	04/2003	Engineering Systems and Computing
Simon Fraser University, Burnaby, British Columbia	PHD	07/2011	Computing Science
Martinos Center, Massachusetts General Hospital, Charlestown, Massachusetts	Postdoctoral Fellow	11/2015	MRI Physics

A. Personal Statement

My academic research has focused on the practical rather than the theoretical.

During my PhD, I designed and implemented a system to acquire and track images of skin lesions, which is still in use at the University of British Columbia's Skin Care Centre. During my Postdoctoral training, my research focused on mitigating the effects of motion in MRI acquisitions, which is the largest obstacle to acquiring quality MRI data in clinical populations. This practical approach to research has given me a unique perspective on the challenges involved in bringing research ideas to the clinic.

Recently, I have taken a non-academic position at CorticoMetrics LLC in order to focus my energies on bringing the brilliance in research to the bedside. In my time at CorticoMetrics, I have investigated and implemented a Continuous Integration testing infrastructure, making use of both Amazon and Google cloud-services, for usage in our FDA 21 CFR Part 820-compliant Quality Management System QMS. I have also implemented a source code control system compliant with our QMS.

In my time at CorticoMetrics, I have drafted the initial software specification of CorticoMetrics first product: a cross-sectional neuromorphomery reporting device. I then designed the software in a manner that naturally harmonizes with IEC 62304. I have also investigated and implemented a Continuous Integration testing infrastructure, making use of both Amazon and Google cloud-services, for usage in our FDA 21 CFR Part 820-compliant Quality Management System QMS.

In the proposed project, I will oversee the translation of FreeSurfer's longitudinal processing stream from it's current state as open-source academic code into a software medical device.

B. Positions and Honors

Positions and Employment

2001 - 2001 Software Developer, National Research Council (NRC), London
2002 - 2002 Research Assistant, University of Guelph, Guelph
2003 - 2004 Application Engineer, Oracle (Formerly Cimmetry), Montreal
2005 - 2006 English Teacher, NOVA Group, Osaka
2006 - 2007 Teaching Assistant, Simon Fraser University, Burnaby
2007 - 2011 Research Assistant, BC Cancer Research Centre, Vancouver
2011 - 2015 Postdoctoral research fellow, MASSACHUSETTS GENERAL HOSPITAL
2015 - present Staff Scientist, CORTICOMETRICS, LLC

Other Experience and Professional Memberships

2012 - present Member, ISMRM
2015 - present Member, RSNA

Honors

1998	Undergraduate Scholarship, VALE (Formerly INCO)
2006	Entrance Scholarship, Simon Fraser University
2007	Student Scholarship, Medical Imaging Perception Society (MIPS)
2008	Best Student Paper Finalist, International Society for Optical Engineering (SPIE)
2008	Research Internship, Mathematics of Information Technology and Complex Systems(MITACS)
2008	Training Scholarship in Skin Research, Canadian Institutes of Health Research (CIHR)
2008	Graduate Scholarship, Simon Fraser University
2009	Charlwood Family Graduate Scholarship, Century 21
2010	Graduate Fellowship, Simon Fraser University
2011	President's Research Stipend, Simon Fraser University
2011	Albert M. Kligman Young Investigator Scholarship, International Society for Biophysics andImaging of the Skin (ISBS)
2014	Educational Stipend, International Society for Magnetic Resonance in Medicine (ISMRM)
2015	Postodctoral Recognition Award, Massachusetts General Postdoctoral Association (MGPA)

C. Contribution to Science

1. My PhD research focused on the Automated Diagnosis of Skin Lesions from digital dermascopic images.

   Traditionally, most methods adopted a computer-aided diagnosis pipeline which includes the following stages: Acquisition, Artifact Detection, Lesion Segmentation, Feature Extraction and Classification. I demonstrated that the use of supervised learning techniques could be used to generalize several of the above stages into a single mathematical model[1,2].

   I also designed a method to calibrate low-cost digital dermoscopes[3], which could significantly reduce to the cost of digital dermoscopy.

   [1] **Wighton, Paul**, Tim K. Lee, Harvey Lui, David McLean, and M. Stella Atkins. "Generalizing common tasks in automated skin lesion diagnosis." Information Technology in Biomedicine, IEEE Transactions on 15, no. 4 (2011): 622-629.

   [2] **Wighton, Paul**, Tim K. Lee, Greg Mori, Harvey Lui, David I. McLean, and M. Stella Atkins. "Conditional random fields and supervised learning in automated skin lesion diagnosis." Journal of Biomedical Imaging 2011 (2011): 8.

   [3] **Wighton, Paul**, Tim K. Lee, Harvey Lui, David McLean, and M. Stella Atkins. "Chromatic aberration correction: an enhancement to the calibration of low-cost digital dermoscopes." Skin Research and Technology 17, no. 3 (2011): 339-347.

2. My Postdoctoral research focuses on technical aspects of MRI acquisition.

   In collaboration with several other research groups, including MGH psychiatry and MIT, I helped to develop software and imaging modalities [1] used to facilitate the development of real-time fMRI neurofeedback therapies. I also developed methods to design successful real-time fMRI experiments based on statistical signal processing [2]. More recently, my research has focused on real-time prospective motion mitigation techniques[3,4]

[1] Hinds, Oliver, **Paul Wighton**, M. Dylan Tisdall, Aaron Hess, Hans Breiter, and Andre Kouwe. "Neurofeedback using functional spectroscopy." International journal of imaging systems and technology 24, no. 2 (2014): 138-148.

[2] Stoeckel, L. E., Kathleen A. Garrison, Satrajit S. Ghosh, **Paul Wighton**, Colleen A. Hanlon, Jodi M. Gilman, Stephanie Greer et al. "Optimizing real time fMRI neurofeedback for therapeutic discovery and development." NeuroImage: Clinical 5 (2014): 245-255.

[3] Adam van Niekerk, **Paul Wighton**, Ali Alhamud, M. Dylan Tisdall, Andre van der Kouwe, Ernesta Meintjes, "A vector based approach for fast real time orientation measurement in magnetic resonance imaging (MRI)." Physica Medica: European Journal of Medical Physics 32 (2016): 158.

[4] **Paul Wighton**, M. Dylan Tisdall, Erez Nevo, Kawin Setsompop, Stephen F. Cauley, Himanshu Bhat, Thomas Benner, Dara S. Manoach, Andre van der Kouwe. "Slice-by-slice prospective hardware motion correction in EPI and simultaneous multislice sequences". Presented at the International Society for Magnetic Resonance in Medicine (ISMRM) 2014, Milan, Italy

D. Research Support

Ongoing support

R01 HD093578-01 van der Kouwe 2017/06 - 2022/06
Neuroimaging and gut microbiome markers of development in HIV-exposed uninfected infants
This project investigates the relationship between maternal HIV infection, breast milk composition, the developing infant gut microbiome, and the developing infant brain.

R42 CA183150-02 Wighton/van der Kouwe (co-PIs) 2017/04 - 2019/04
AutoRegister: A system for enhancing the accuracy of tumor change detection
The goal of the resulting system is to automate the alignment of a patient's brain scan with that of a prior scan such that subsequent offline tumor measurements do not have error introduced solely by differing slice orientations.
Role: PI

Past support

[redacted] Manoach/Van De Ville (co-PIs) 2015/03 - 2018/03
Dynamics of Brain Networks in Children with Autism: from Motion-Corrected Imaging through Network Analysis to Prediction of Effective Treatment Response
The goal of this project is to understand the neurocorrelates of autism by scanning a cohort with motion-robust MRI technology suitable for imaging autistic children.
Role: Research Scientist

R41 AG052246-01 Schmansky/Sabuncu (PD/PI) 2015/09 - 2017/08
A Structural Brain MRI Dementia Forecast Tool
The proposal is to build software tools that will predict amyloid status and forecast future clinical progression toward AD dementia. The tools, which examine measures derived from an MRI scan, will be invaluable for pre-screening, stratifying, and tracking individuals recruited for preclinical AD trials, and will offer substantial cost savings by reducing the number of PET scans necessary to identify amyloid-positive cognitively normal individuals. Additionally, the project will involve code development in an FDA compliant manner.
Role: Research Scientist

R44 NS089090-01A1 Schmansky/Fischl (PD/PI) 2015/09 - 2018/08
MRI brain morphometry for computer-aided detection of neurological disorders
In this project we seek to (1) integrate novel deep-learning and Random Forest-based patch-matching image synthesis technology into FreeSurfer to make it robust to variations in scanner platform and acquisition parameters, (2) use modern parallel-processing to reduce execution time to a clinically-feasible length, and (3) develop the code in an FDA compliant manner.

Role: Research Scientist

[redacted] Manoach/Whitfield-Gabrieli (co-PIs) 2015/01 - 2015/12
Development of accelerated diffusion and functional MRI scans with real-time motion tracking for children with autism
The goal of this project is to develop motion-robust MRI technology suitable for imaging autistic children
Role: Postdoctoral Research Fellow

R01HD071664: van der Kouwe (PI) 2015/07 - 2015/10
Longitudinal Neuroimaging and Cognitive Study of HIV-Infected Children
The goal of this project was to understand the neurocorrelates and brain development of children born with HIV
Role: Postdoctoral Research Fellow

R21MH096559: van der Kouwe (PI) 2012/06 - 2014/05
Technology development and neuroimaging for 5 year old children with HIV infection
The goal of this project was to understand the neurocorrelates and effects of antiretroviral treatment (ART) on children born with HIV
Role: Postdoctoral Research Fellow

R21/33DA026104 van der Kouwe / Breiter (co-PIs) 2011/09 - 2013/06
Functional Spectroscopy with Real-Time Feedback for Altering Preferences in Addiction
The goal of this project was to develop novel therapeutics for drug addition using real-time fMRI (rt-fMRI) technology
Role: Postdoctoral Research Fellow

EQUIPMENT

Project/Performance Site Primary Location and Location 1

For the proposed project ‘Unbiased longitudinal neuromorphometry for clinical decision support', standard PC hardware and software is the only necessary equipment for development. CorticoMetrics has such machines and software on-site.

Project/Performance Site Location 2

MGH Equipment used in this project (reference Facilities and Resources, notably the Computing Facilities and Administration Area):

Computing Facilities

Administration Area

A. Specific Aims

Normal human neuroanatomy is tremendously variable, and variability increases with age[1-3]. This impedes the ability of neuroimaging to detect effects in neurological conditions such as Alzheimer's disease (AD)[4-11], Huntington's disease[12-14] (HD), multiple sclerosis[15] (MS) and schizophrenia[16-18]. Most of the most recently available state-of-the-art quantitative imaging tools still naively use cross-sectional methods to analyze repeated scans. These tools lack the sensitivity to monitor subtle progressive changes because such approaches do not account for the large intrinsic variability of normal neuroanatomy. The goal of this project is to commercialize a longitudinal, neuro-morphometric image processing pipeline for use in radiology, neurology and related clinical fields. The successful completion of this project will result in an FDA 510k-approved MRI neuro-morphometric longitudinal analysis stream with more statistical power than is currently available. This increase in power will directly translate into an enhanced ability to detect and assess progression at both the individual and group levels. It will also alleviate a major pain point in current longitudinal neuroradiology reading workflows, reducing radiology report turnaround times (RTAT).

Phase 1 Aims:

Aim 1: Integrate the FreeSurfer longitudinal code into CorticoMetrics' compute infrastructure.
Subaim 1.1: Migrate the FreeSurfer longitudinal code to a formal compute environment (docker)
Subaim 1.2: Migrate the FreeSurfer longitudinal pipeline to a formal execution environment (cwl)
Subaim 1.3: Create initial unit, integration, system test sets and continuous integration (CI) framework
Aim 2: Draft initial versions of CFR 820.30(c) compliant design input documents (SRS/SAD/SDD)
Aim 3: Conduct Phase 1 feasibility study
Deliverable: Validation of feasibility of the pipeline after migration to CorticoMetrics' infrastructure

Phase 2 Aims:

Aim 1. **Improve longitudinal pipeline execution time in preparation for clinical use cases; extend pipeline functionality**
Subaim 1.1: Identify and optimize modules of code, ordered by impact
Subaim 1.2*:* Add hippocampal subfield and amygdalar nuclei segmentation functionality to the pipeline
Subaim 1.3: Add future timepoint prediction functionality to the pipeline
Deliverable: An accelerated pipeline with a 15-minute total execution time on a single cloud instance.
Aim 2. Integrate the longitudinal pipeline with the AutoRegister tool for slice-prescriptioning.
Subaim 2.1. Retrieve previous scans from the PACS, prescribe new scans in longitudinal coordinate system, tag as a longitudinal scan.
Subaim 2.2. Add longitudinal semantics to data generated by AutoRegister
Subaim 2.3. Use AutoRegister to prescribe high-resolution scans for subfield/nuclear segmentation.
Deliverable: A scanner tool to help maximize the power of longitudinal studies (not part of initial 510k submission)
Aim 3: **Produce an accelerated, automated longitudinal stream that is FDA cleared**.
Subaim 3.1: Draft remaining documents required by CFR 820.30(c) (Verification/Validation/Risk/Usability)
Subaim 3.2: Perform design reviews (input/code/risk/verification/validation) and make resulting changes
Subaim 3.3: Execute Verification/Validation/Usability plans and submit for FDA 510(k) approval
Deliverable: FDA 510(k) cleared commercial software for automatically generating longitudinal neuromorphometry reports.

B. Research Strategy

B1. Significance

The year 2018 began with a sobering reminder of how difficult it is to develop drugs for some of the world's most terrifying diseases. On January 8th, Pfizer announced that it would discontinue its research into drug discovery to treat Alzheimer's and Parkinson's diseases[19]. On the very same day, Axovant Sciences announced that its new experimental drug had failed to treat dementia[20]. A day later, the Journal of the American Medical Association (JAMA) published results indicating another drug had failed to treat Alzheimer's disease[21].

A month later, the FDA released five draft guidance documents, indicating their intent to change their approach to advancing treatments for neurological disorders that aren't adequately addressed by available therapies[22]. Of particular interest is the draft guidance for the development of drugs to treat early Alzheimer's disease[23] which states that a biomarker alone is a sufficient endpoint for a successful clinical trial. This is a prominent departure from previous guidelines which required that a drug demonstrate both cognitive and functional improvements.

Imaging biomarkers will play an increasingly essential role in the diagnosis, monitoring and treatment of neurodegenerative disorders. Yet identifying reliable neuroimaging biomarkers has been notoriously difficult. Brain anatomy is enormously variable and inter-subject variance is commonly recognized to be the single largest source of "noise" in neuroimaging studies. This decreases statistical power and inhibits detection and monitoring efforts. For example, Figure 1 summarizes results from a neuro-morphometric MRI study of Alzheimer's disease (AD) and age-matched controls (OC). The left 2 plots (blue circles) represents elderly control subjects (OC, N=52) and age-matched Alzheimer's subjects (AD, N=27) from the Alzheimer's Disease Neuroimaging Initiative (ADNI)[24]. While, there is a statistically significant difference between the group means, the overlap between groups is substantial. However, in a one-year follow-up study of the same subjects, the longitudinal change in ventricular volume, as assessed with our currently available longitudinal methods, demonstrated greater discrimination across groups (Figure 1, Green). The greater sensitivity corresponds roughly to a **4-fold improvement in discrimination relative to what is afforded using cross-sectional approaches**, which would further increase as the time between follow-up scans increases since this would add additional power to our longitudinal method relative to cross-sectional methods. The goal of this proposal is to translate this technology to the clinic by seeking 510(k) clearance for a software only medical device to automatically generate longitudinal neuromorphometry reports. The device will be based on methods and software that have been freely available to researchers since 2009 and whose associated methods papers have been cited approximately 1500 times[25-28] yet re-engineered to meet the rigor of regulatory requirements. In addition to providing the ability to automatically detect clinically relevant changes at the individual and group levels, this proposal would also improve neuroradiology reading room efficiency. Clinical radiologists reading follow-up scans spend most of their time scrolling through the slices of the subsequent time-point(s) to try to find a comparable slice as the baseline or previous scan. For geometrically complex structures such as the cortex, ventricles or even the hippocampus, this process is tedious and error-prone as even small differences in head position prevents accurate slice-matching. Some decision support tools allow registration and reslicing of subsequent scans. However, as is now widely understood in the research community, this process introduces bias as the resampling of subsequent time points introduces additional smoothness relative to the baseline, introducing apparent effects where none exists. In contrast, our "midspace" tools and AutoRegister automated slice prescriptioning device (see sections B.2.2 and B.2.5 respectively for details), will completely remove the

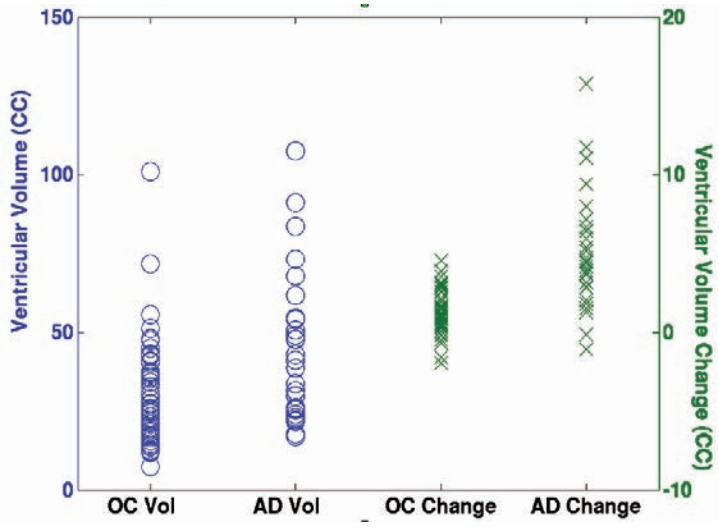

Figure 1 Left (blue circles) ventricular volume for old controls (OC) and Alzheimer's subjects (AD). Right (green X), changes in ventricular volume after one year showing significantly increased separation of the groups.

bias and dramatically reduce the time it takes clinicians to read longitudinally acquired images. Further, our tool will be the only existing clinical utility that is not limited to pairs of images, but instead can process any number of longitudinal images[25] allowing clinicians to accurately detect slow progression over multiple scan sessions. These innovative methods, which have repeatedly demonstrated the ability to increase statistical power and diagnostic accuracy could inform us about the onset and progression of neurodegenerative disorders and, by extension increase the quality of patient care while improving upon the efficiency of clinical trials and neuroradiology reading times.

Impact and Clinical Relevance

Longitudinal change in hippocampal volume, as measure by structural MRI, is best performing biomarker as an outcome measure for clinical trials in patients with mild cognitive impairment (MCI), an early indication of Alzheimer's disease[29]. FreeSurfer is a set of freely available, open-source algorithms for the structural analysis of MRI neuroimaging data and is in use by over 32,000 researchers and clinicians (see Figure 2). Our existing longitudinal analysis stream (which we are proposing to commercialize) has become one of the main tools used for analyzing the Alzheimer's Disease Neuroimaging Initiative (ADNI) data, and has resulted in a better understanding of the time-course of anatomical changes early in the disease[7, 30]. The FreeSurfer longitudinal stream has also been a main tool for understanding the extensive cortical changes that occur in HD and have resulted in a paradigm shift in how that disorder is conceived[12-14, 31].

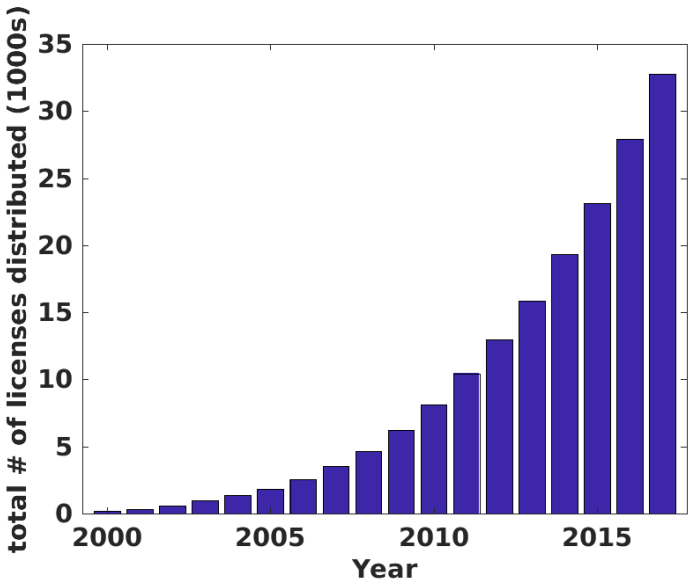

Figure 2 Cumulative FreeSurfer licenses distributed since 2000

These are examples of the large community of clinicians using FreeSurfer to investigate an array of disorders[2, 12, 13, 18, 31-36]. These users represent a ready-made user-base for our proposed FDA-cleared longitudinal analysis product. Additionally, clinicians spend a disproportionate amount of their time attempting to visually assess longitudinal changes in neuroanatomical structures - a process that would be made substantially easier and more sensitive with the proposed tools.

Probability of commercialization

Our longstanding roots in the academic neuroimaging world, coupled with our industry partners (MGH, Siemens, EnvoyAI) substantially enhances the probability of commercialization. These relationships are described further in the Commercialization Plan and Letters of Support. Additionally, after working closely with regulatory advisors, we have designed a technology stack harmonized with IEC 62304 guidelines and uniquely suited to translating image processing pipelines into class II software only medical devices. This is described further in section B.2.1.

B2. Innovation

In this section, we discuss the novelties of CorticoMetrics' compute infrastructure designed to adhere to regulatory requirements, the innovations in FreeSurfer's state of the art longitudinal processing stream, as well as the integration with another clinical device product under development at CorticoMetrics: AutoRegister.

B.2.1 CorticoMetrics' compute infrastructure

For the past 2 years, CorticoMetrics has been developing its compute infrastructure to facilitate the translation of academic image processing pipelines into software-only, batch processing medical devices for clinical use. The two major challenges encountered were 'hardening' the code so that it is suitable for enterprise applications and adhering to the strict regulatory requirements for development of clinical software. CorticoMetrics' infrastructure is built on top of two emerging technologies, both of which help overcome each of the challenges encountered: docker and the common workflow language. Both technologies formalize the execution environment and are examples of "Literate Programming"[37] (more recently known as "Documentation as Code"[38])

Docker

Docker is an open source software project that provides the industry-leading implementation of the open container initiative[39] container specification[40]. Container technology offers a simple, fast, and robust way for developing, distributing, and running software. Conceptually, a container is like a virtual machine: it provides a comprehensive account of the computing environment, ensuring consistent deployment and results across computing infrastructure. While conceptually similar to a virtual machine, there are however several technical advantages to containers over virtual machines. All CorticoMetrics' software is developed and delivered inside docker containers. This provides us with explicit documentation of the computing environment, ensuring reproducible results across compute infrastructure which substantially mitigates risk. Also, data provenance is easily established by recording which docker container was used to process which data. Container technology is currently experiencing massive adoption. All major cloud providers currently support the execution of docker containers. It is estimated the market for application containers will be [redacted] by 2020[41]. CorticoMetrics' strategic partner for clinical deployment (EnvoyAI) also supports the execution of docker containers.

The Common Workflow Language

The Common Workflow Language (CWL) is a specification for describing analysis workflows in a way that makes them portable and scalable across software and hardware environments. CWL builds upon existing state of the art technologies including JSON-LD and Docker. CWL isolates execution tasks and enforces explicit definitions of inputs and outputs.
The benefit of explicitness and isolation are flexibility, portability, and scalability: tools and workflows described with CWL can transparently leverage technologies such as Docker and be used with CWL implementations from different vendors. CWL is well suited for describing large-scale workflows in cluster, cloud and high performance computing environments where tasks are scheduled in parallel across many nodes[42].
CorticoMetrics is leveraging CWL to ensure scalability, portability and reproducibility of results. Execution isolation is also used to mitigate regulatory risk. Finally, the common workflow language offers a natural framework for structuring our software development process in harmony with international standards (IEC 62304). CorticoMetrics has developed infrastructure to automatically regenerate regulatory documents, such as the software architecture document (aka SAD, as per IEC 62304-5.3) and software design document (aka SDD, as per IEC 62304-5.4) when the pipeline is modified by automatically parsing the cwl workflow graph. Additionally, CorticoMetrics has structured it's tests of cwl workflows to harmonize with international software verification standards (IEC 62304-5.5.1 to 5.5.3 and 5.5.5)

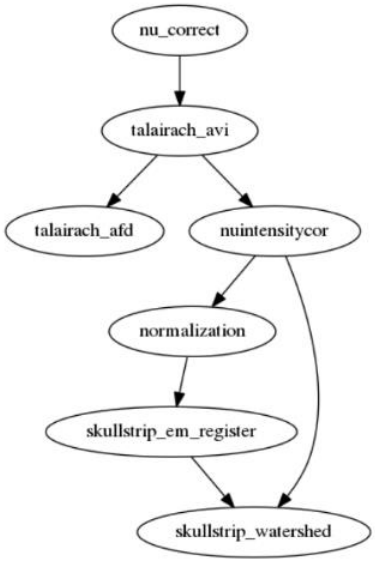

Figure 3 The beginning of FreeSurfer's recon-all stream as expressed as a (cwl) workflow. The cwl provides scalability, reproducibility, and a structure that harmonizes naturally with IEC 62304

B.2.2 FreeSurfer's novel longitudinal image processing pipeline

One simplistic approach to longitudinal data analysis is to treat each time point independently and conduct a post-hoc comparison of measurements from different time points. While this approach is unbiased (since all time points are treated the same), a more powerful approach would be to utilize the information that the anatomy being imaged is from the same subject over time. One way of achieving this is by directly co-registering the scans from different time points, or using a subject-specific or universal deformable template[43, 44]. A problem of these methods is that the results depend on the amount of regularization used in the construction of the deformations. Another critical issue is the potential introduction of bias into the analysis. That is, if the analysis of two time-points depends on the temporal ordering of the scans, it risks introducing spurious effects. Ensuring “inverse consistency”[45] alleviates this issue. In general, inverse consistency implies that if the temporal ordering is reversed then the estimated effects should be exactly reversed as well. A lack of inverse consistency has been shown to introduce bias into the estimation of AD effects[46] and in test-retest analysis[25].

An implication of inverse consistency is that one must pay attention to the coordinate system in which the analysis of change occurs. For example, even if a registration is inverse consistent, if one time point is resampled to be in the coordinate system of another time point, bias and spurious findings will result due to the difference in the way the two images are processed. The image that is resampled will be smoother than the one that is not, resulting in apparent differences in derived morphometric values such as volume and thickness. To avoid this problem, current research tools utilize “midspace” or “halfway” coordinate systems, that enable both images to be transformed “half way”, instantiating an unbiased coordinate system. In recent work, we have generalized this concept to work with an arbitrary number of scans of an individual over time, allowing a flexible, unbiased, longitudinal coordinate system to be built[25].

Another critical issue that must be addressed is the recovery of a rigid transform that aligns two images in the presence of differences in image content. For example, in subjects with putative AD, a clinician acquires multiple images explicitly to detect potential changes in the anatomy. A useful registration technique must therefore be able to generate an accurate alignment in the presence of true anatomical change. This problem is further complicated by the fact that multiple regions of a typical image will not be alignable with a rigid transform as e.g. the tongue/jaw/eyes/etc will have a different appearance in subsequent scan sessions. Thus, the ideal registration technique would seek to accurately align some portions of the image (e.g. the skull), while allowing the alignment in other regions, such as the tongue and jaw, to be arbitrary.

We have developed a novel registration method[25, 27] based on robust statistics that addresses these issues, and accurately aligns images in the presence of these differences in image content. The proposed technique detects and ignores outlier regions, i.e. differences that are not due to positional (transformation) changes. This method is designed to be inverse consistent, which is necessary to keep the registration unbiased. We achieve this goal through a symmetric displacement model, and by resampling both source and target to an unbiased halfway space in intermediate steps. In [26] we demonstrated improved registration accuracy compared to state-of-the art tools such as those of FSL[47] and SPM[48]. Registration performance was quantified with respect to a ground truth transformation and using both test/retest and synthetic data. Our results[25, 27] demonstrate that the proposed robust registration strategy produces significantly more accurate alignments, and critically for use in neurodegenerative disease, is insensitive to atrophic changes in the subject’s anatomy, and can be used to analyze an arbitrary number of timepoints.

In addition to the robust registration, the FreeSurfer longitudinal processing stream contains other innovative algorithms that maximize power without introducing bias. For example, temporal information is fused using a Parzen window approach that uses the multiple images to reduce noise in regions of no anatomical change, but preserves image information in regions of e.g. brain atrophy. Cross-sectional segmentation information is fused using a similar approach, increasing robustness and reliability without sacrificing sensitivity. Finally, cortical thickness measures are computed using an explicitly longitudinal approach in which the correspondences between the gray/white and pial surfaces are fixed in a spherical coordinate system, while

the distance between corresponding points is used to compute the thickness, again increasing reliability while retaining sensitivity to the disease effects we wish to quantify.
These innovations have been rigorously validated on a variety of datasets in and in a variety of scenarios[25]. Figure 3 illustrates test-retest results in a n=115, 2-timpoint dataset where timepoints were collected in the same session, which implies a ground truth of no morphometric changes.

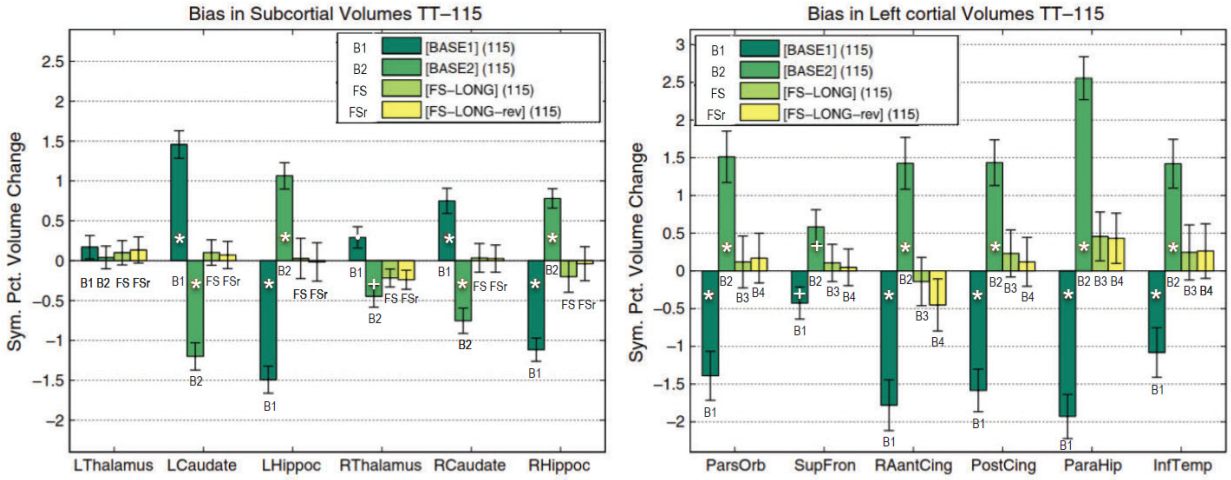

Figure 4 Test-retest results on a dataset where ground truth is no morphometric changes. Swapping timepoints reveals a bias in symmetrized percent change. Our method [FS-LONG] and does not induce this bias.

B.2.3 Hippocampal subfield and amygdalar nuclei segmentation

The hippocampus and amygdala consist of several distinct regions, known as *subfields* and *nuclei* respectively, that are differentially affected by AD[49, 50]. These structurally and functionally diverse anatomical regions have been traditionally treated as a single structure under MRI, however recent advances in high-resolution MR imaging have made it possible to study hippocampal and amygdalar subregions *in vivo*. Incorporating work performed under the supervision of Bruce Fischl and Martin Reuter (co-PI and advisor on this grant respectively) to augment our pipeline with the ability to perform longitudinal hippocampal and amygdalar subfield/nuclei segmentation[51] will provide clinicians with a richer set of potential AD biomarkers and further inform the understanding of the progression of AD. Information from subfields and nuclei have been shown to improve the ability to diagnose AD[52], and further, incorporating explicit longitudinal modeling into the segmentation allows the differentiation of early MCI from both controls and AD subjects, a critical distinction that could not be detected using cross-sectional methods[51].

B.2.4 Future timepoint prediction

It is widely believed that the onset of the underlying pathology for AD begins years, if not decades, prior to the appearance of clinical symptoms[53]. While a cure for AD remains elusive, any intervention that could delay disease onset or progression would represent a significant alleviation of its healthcare burden[54],[55]. A method to predict the onset of AD would therefore be a valuable tool in the clinician's arsenal. While predicting future changes in neuromorphometry alone may not be sufficient for a reliable AD predictor, it may serve as one of several critical components or further understand the underlying mechanisms of AD and inform early diagnosis.
We will explore methods to augment our longitudinal pipeline with the means to predict a subject's neuromorphometrics at an arbitrary time in the future from as little as a single timepoint. While more conventional mixed effects models have been shown to improve estimation of subject-specific longitudinal trends by using inter-population similarity[56, 57], they require multiple observations for any given subject, and do not attempt to provide subject-specific predictions from a single observation.

B.2.5 The AutoRegister slice prescription tool

The clinical burden of motion in MR imaging is, by extremely conservative estimates, at least 1.77 billion dollars per year in the US alone[58] (see commercialization plan for details). CorticoMetrics is targeting this market with a clinical device called AutoRegister. When a patient is registered for an MRI session, AutoRegister automatically retrieves imaging data from the patient's previous sessions and automatically sets imaging field of view (FOV) parameters on the MRI scanner. This process is often referred to as *slice prescription*. Aligning the FOV with those from previous scans at acquisition time ensures that image volumes are in alignment when they get to the radiology department, without any further workflow intervention or data manipulation/degradation. This will dramatically reduce radiology report turnaround times (RTAT), as metric of paramount import in any radiology department radiology department.

While the development of AutoRegister is outside the scope of this proposal, there are complementary aspects that make this longitudinal analysis we propose in this project significantly synergistic with the existing AutoRegister tool. Our novel longitudinal analysis stream makes use of a “midpoint space” to ensure inverse consistency and unbiased metrics (as described in B.2.2). It can be shown that prescribing follow-up scans with an FOV of this midpoint space will **maximize the power of any longitudinal study**, as no further transformations (which subtly degrade the data) need be applied. Additionally, in current longitudinal studies, the RMS distance from the midpoint space to the acquisition spaces increases as time points are added to the study. Introducing AutoRegister into the acquisition pipeline of ongoing longitudinal studies will ensure this RMS distance will never increase, obviating the need for any resampling (which reduces effective resolution), further increasing the power of the study.

Additionally, high resolution imaging of the hippocampus and amygdala requires a highly skilled MR technician and a compliant subject to align a rather narrow, yet high-resolution FOV: a task AutoRegister has been designed to solve. Integrating this sequence into AutoRegister will allow the technique to be applied more broadly, rapidly and accurately.

B.2.6 The Big Picture

The tools we propose to develop here represent a small step towards a larger goal of revolutionizing healthcare. CorticoMetrics believes the future of healthcare lies at the intersection of **personalized medicine** and **machine intelligence for decision support** and uses these guiding principles to develop all its products. How these tools fit into CorticoMetrics’ larger vision for the future of healthcare is further described in the Commercialization Plan.

B.3. Approach

B.3.1 Phase I Approach

The goal of Phase I is to demonstrate the feasibility of this proposal. We will accomplish this by migrating the existing software to CorticoMetrics’ compute infrastructure, drafting CFR 820.30(c) compliant design documents, and re-validating the new codebase using previously established statistical methods. A timeline of the proposed Phase I activities is illustrated in Figure 5. While we will carry out these feasibility studies to ensure that the tools continue to function at a high level, we stress that this is a “low risk” proposal in that every tool we intend to make clinically usable has already been employed by dozens of studies quantifying the effects of an array of neurodegenerative disorders in institutions across the world[2, 12, 13, 18, 31-36].

Phase 1, Aim 1: Integrate longitudinal code into CorticoMetrics’ compute infrastructure.

We will begin the project by migrating the existing software to CorticoMetrics compute infrastructure. This includes ‘dockerizing’ the application, re-implementing the workflow logic in the common workflow language (cwl) and writing the initial test set and integrating it into CorticoMetrics’ continuous integration (CI) environment. CorticoMetrics’ compute infrastructure is further described in section B.2.1

Subaim 1.1: Migrate the FreeSurfer longitudinal code to a formal compute environment (docker)

Here, we 'dockerize' the software by explicitly defining the environment in which it will run and crafting a 'container' for the software. As described in B.2.1, this will ensure reproducibility and provenance of results and aid in the regulatory documentation effort. CorticoMetrics has extensive experience in dockerizing academic software. In fact, we make freely available FreeSurfer docker containers as a service to the community and to promote best practices[59]. We expect this process to take no longer than 64 developer hours (one person devoting 20% effort for 2 months).

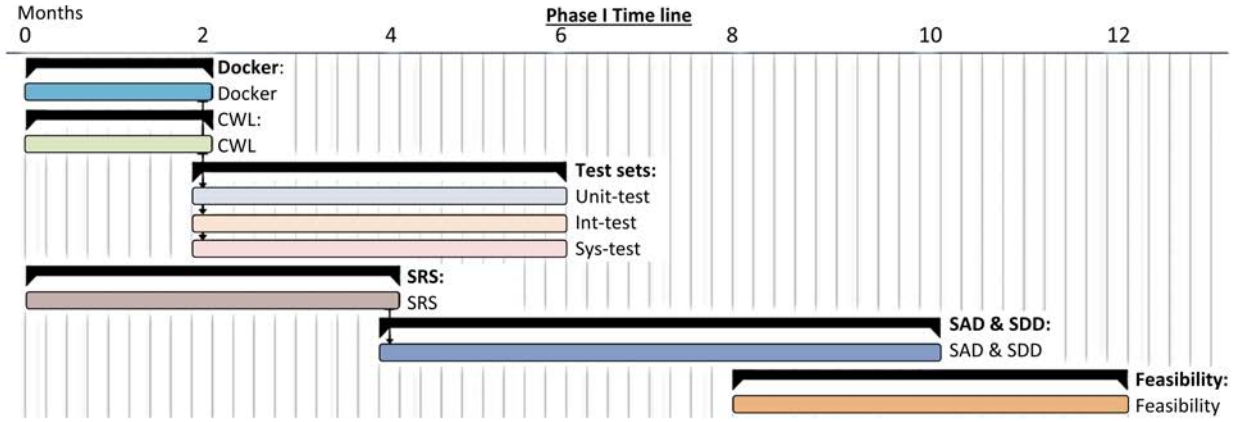

Figure 5 Phase I timeline (0-12 months)

Subaim 1.2: Migrate the FreeSurfer longitudinal pipeline to a formal execution environment (cwl)

In this subaim, we migrate the existing longitudinal pipeline, currently written in c-shell scripts, to the common workflow language (cwl). As described in section B.2.1, the cwl is a state of the art specification for describing batch processing workflows that offers a number of benefits including: scalability, portability, task execution isolation, visualization, documentation and risk mitigation. CorticoMetrics has already performed this process on FreeSurfer's cross sectional stream.

Since there is significant overlap in FreeSurfer's cross sectional and longitudinal streams, we expect this process to take a skilled cwl developer no longer than 256 developer hours (one person devoting 40% effort for 4 months)

Subaim 1.3: Create initial unit, integration, system test sets and continuous integration (CI) framework

Once the workflow has been migrated to a docker container, and re-written in the common workflow language, we will create and integrate a test set into CorticoMetrics' continuous integration (CI) framework. Continuous Integration is a software development practice where members of a team integrate their work frequently, often multiple times a day. Each integration is verified by an automated build and test to detect integration errors as quickly as possible. This approach leads to significantly reduced integration problems and allows a team to develop cohesive software more rapidly[60].

In addition to helping CorticoMetricis develop software more efficiently, we intend to use this test set as the basis for the CFR 820.30(c) verification plan that we will draft and execute in Phase II. We therefore adopt IEC 62304 guidelines (sections 5.5-5.7) and structure our tests accordingly. IEC 62304, the international standard for software development in medical devices, requires the establishment of objective acceptance criteria for each test. It also suggests structuring tests into three sets: unit, integration and system. The common workflow language provides a natural framework for crafting these three tests sets. In the context of a batch processing pipeline described by a cwl workflow, unit tests are tests of individual *cwl steps*, integration tests are tests of cwl *sub-workflows*, and system tests are end-to-end tests of the the *cwl master workflow*. Tests will be written in the *bash automated testing system* (bats) and executed in circleCI enterprise.

This subaim represents the largest work effort during phase I. We expect it will take approximately 576 software QA engineering hours to complete (one software QA engineer devoting 60% effort for 6 months)

Phase 1, Aim 2: Draft initial versions of design input documents

In this aim, we complement the technical developments in Aim 1 with documentation efforts by creating initial drafts of the *design input documents*, as required by CFR 820.30(c). As in Aim I, we adopt international best practices and structure our *design input documents* as suggested by IEC 62304 into the *software requirements specification* document (SRS; as per IEC 62304-5.2), the *software architecture document* (SAD; as per IEC 62304-5.3) and the *software detail design* document (SDD; as per IEC 62304-5.4).

Subaim 2.1: Draft Initial version of the software requirements specification (SRS) document

The SRS is the foundational document of any software only medical device. Careful planning is required at this stage to minimize potential downstream regulatory, technical, and logistical complications. We will rely on our consultants to advise us on regulatory issues and out network of clinical and technical professionals to advise us on design and use cases.
Due to the central import of this document, careful drafting, review and scrutiny should not be rushed. We estimate it will take a software architect familiar with the application domain 128 hours (one software architect devoting 20% effort for 4 months) to draft and review

Subaim 2.2: Draft initial versions of SAD/SDD

According to ICE 62304, the two *design inputs* in addition to the SRS are the Software Architecture Document (SAD) and the Software Details Design (SDD). CorticoMetrics has structured its development guidelines to automatically generate large portions of these documents. Once the workflow has been formally defined using the common workflow language, the resulting data structure (known as a DAG: directed acyclic graph) is parsed for a specific subset of cwl-1.0 tags that are used to generate documentation in markdown format. Since this subaim is already complete and essentially automated, we anticipate it will take a technical writer a minimal amount of time to collate and proofread the auto generated data to create the SAD and SDD. We budget 32 hours (2 hours per week for 16 weeks) for a technical writer to collate these documents and an additional 32 hours (2 hours per week for 16 weeks) for a junior developer to maintain and improve these development guidelines.

Phase 1, Aim 3: Conduct Phase 1 feasibility study

The goal of Phase I of the project is to demonstrate feasibility of the proposed medical device. To do so, we will validate the device, after aim I migration activities have been completed, using the same dataset and methodology used to validate the original longitudinal pipeline. We will reprocess 4 datasets used for the initial validation (TT-115, TT-14, OA-136, HD-54, described in[25]) using our newly ported processing pipeline. We will monitor and save execution times for each node in the cwl workflow graph for use in Phase II, Aim 1.1. The objective pass/fail criteria for the feasibility study will consist of two components: 1) the validation criteria as defined by the validation plan of CorticoMetrics initial 510k via Dice scores, and 2) The computation of 'symmetric percent volume change' (SPVC) as defined in[61]. The first pass/fail criterion ensures that the volume of major subcortical structures agree with expertly labeled data (Dice > 0.8). This is the validation criteria used by our predicate device (NeuroQuant; K170981) and confirmed as reasonable in a pre-submission meeting CorticoMetrics had with the FDA in June 2018 to discuss our 510k submission strategy for our initial product: a cross-sectional neuromorphometric analysis pipeline. The second pass/fail criterion ensures that the longitudinal stream does not induce a timepoint ordering bias (SPVC < 0.01). These objective pass/fail criteria will serve as the basis for the validation plan to be drafted and executed in Phase 2, Aim 3. Since the datasets have already been curated, and the analysis scripts already implemented, we expect validation efforts to take no longer than 128 data scientist hours (one data scientist devoting 20% effort for 4 months)

Phase 1 Deliverables

By the end of the first year of the project, we intend to deliver:

- A working prototype of the software medical device, running in an environment amenable to the demands of enterprise workloads and regulatory control.
- Initial drafts of CFR 820.30(c) compliant design documents including
  - Software Requirements Specification (SRS)
  - Software Architecture Document (SAD)
  - Software Design Document (SDD)
- A test set for the prototype, integrated into CorticoMetrics continuous integration (CI) system. This test set will serve as the initial draft and working implementation of the CFR 820.30(c) compliant verification plan.
- A validation of the software medical device, after being migrated. The validation methods and dataset will match the original academic validation of the method[25]. This validation will serve as the initial draft and working implementation of the CFR 820.30(c) compliant validation plan.

B.3.2 Phase 2 Approach

In Phase II, we continue to prepare the software for commercialization by improving the execution time, integrating it with another CorticoMetrics's offering, AutoRegister, expanding the validation effort and submitting for FDA 510k clearance.

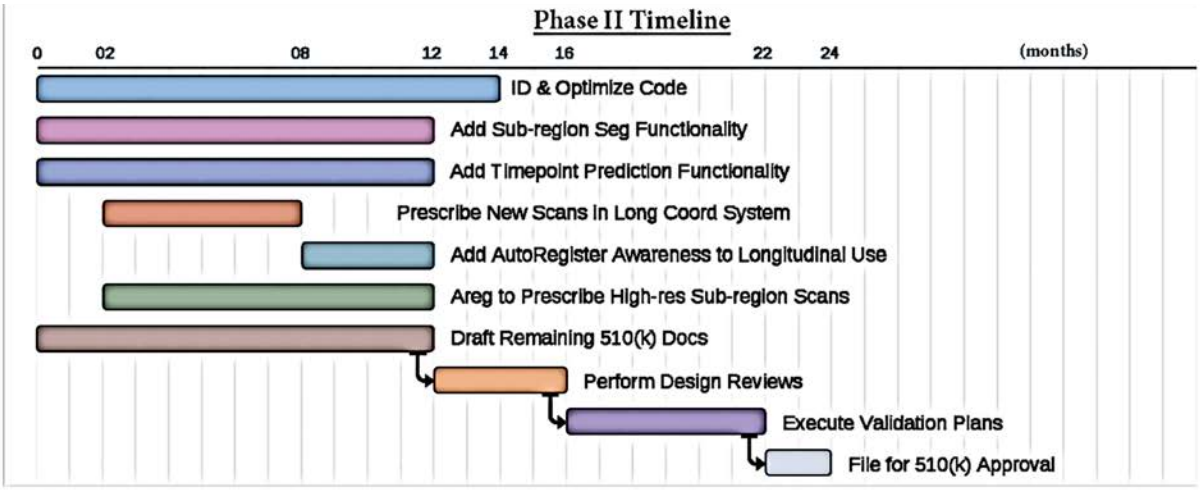

Figure 6 Phase II timeline (0-24 months)

Phase 2, Aim 1: Improve longitudinal pipeline execution time; extend pipeline functionality

The ultimate deliverable of a radiology department is the radiology report. Radiology stakeholders are increasingly demanding faster report turnaround times (RTAT). Anything that delays delivery of the finalized report undermines the value of a radiology department. Since the dominant use case of our device is to produce a report that helps a radiologist to draft radiology reports, ensuring a quick device execution time is critical to the clinical adoption of the product.

The latest release of the research software FreeSurfer (v6.0) takes approximately 6-10 hours to run on typical commercial hardware. CorticoMetrics' initial marketing research has indicated this to be the greatest barrier to clinical adoption. Over the past year, CorticoMetrics has been translating FreeSurfer's cross-sectional analysis stream into a software-only batch processing medical device. During that time, CorticoMetrics has improved the execution time of the stream from 5-10 hours to 1 hour. In this section, we describe the process for improving execution time which we will apply to FreeSurfer's longitudinal stream as well as how we augment the longitudinal stream with the ability to perform subfield hippocampal segmentation and future timepoint prediction.

Phase 2, Subaim 1.1: Identify modules of code to optimize, order by impact

We begin by identifying modules of code which are potential candidates for optimization. Timing data generated during the Phase I feasibility study will be used to identify the nodes in the workflow where most of computation time is being spent. The code these candidate nodes execute will then be *profiled* to determine the potential impact of optimization by measuring the frequency and duration of each function call throughout the execution. An ideal candidate for optimization would be a node that takes a long time to process, and in which most of the nodes time is spend executing a small set of functions. Results from the formal execution structure developed in Phase I, as well as the timing information saved from the Phase I feasibility study can be used here. We therefore estimate this subaim will data a data scientist no more than 64 hours to complete (one person devoting 20% effort for 2 months)

Once suitable modules for optimization have been identified, a suitable optimization strategy must be chosen. To date, the most successful optimization strategies for FreeSurfer have been paralization via OpenMP[62] and GPU[63] programming.

OpenMP (Open Multi-Processing) is a framework for multi-platform shared memory multiprocessing which has been successfully used to convert single-threaded FreeSurfer operations into multi-threaded equivalents. For example, one of FreeSurfer's registration tool's execution time (`mri_em_register`) has more than halved after being parallelized with OpenMP.

GPU (Graphics Processing Unit) architecture was designed to more rapidly manipulate and alter memory. As such, certain operations run considerably faster on GPUs compared to CPUs. An iconic example of this is the 3d convolution operator: a foundational operation in modern neural networks and used ubiquitously throughout medical image processing. Recently, a collaborator (Richard Edgar) managed to optimize one of FreeSurfer's registration tools (`mri_ca_register`) by introducing support for GPU execution, improving performance by over 20%.

Once suitable modules and optimization strategies have been determined, the development work may begin. CorticoMetrics' continuous integration (CI) infrastructure along with the test sets created during phase I will be critical to ensure that optimizations do not negatively impact the pipeline. As this effort could take an indefinite amount of time, we place a hard cap on the development hours used to achieve this submaim, and will continually review decisions made in subaim's 1.1 and 1.2 to ensure time is spent most effectively. We will spend no more than 832 hours (one developer devoting 40% effort for one year) on this activity.

This subaim will be considered a success if the entire longitudinal pipeline with 2 timepoints can be run in less than 120 minutes.

Phase 2, Subaim 1.2 Add hippocampal and amygdalar subregion segmentation functionality to the pipeline

The longitudinal subfield segmentation model relies on a Bayesian inference algorithm within a generative framework, which has already been incorporated into our cross-sectional analysis pipeline. In previous translational work, CorticoMetrics employed the services of Innolitics to port the cross-sectional Bayesian inference algorithm from prototype Matlab code into python. They are already familiar with the algorithm and its underlying technical details and are ideally suited to perform the same task for this application. A letter of support from Innolitics is included with this submission. The model also relies on algorithms in the longitudinal pipeline that we propose to incorporate in this project. It uses an atlas constructed from both high-resolution *in vivo* MRI scans as well as ultra-high-resolution *ex vivo* MRI, which enables detailed manual segmentations that results in a much more accurate atlas. The generative nature of the algorithm allows the application of *ex vivo* atlases to the segmentation of *in vivo* scans since the model does not assume that the intensity characteristics are similar between the training and test datasets.

We expect this aim will take an outside contractor with software engineering experience no more than 1040 hours (50% time for 1 year) to complete.

The criteria for success for this subaim will mirror that of the phase I feasibility study and our 510k validation plan: An average Dice score greater than 0.8 across the subfields and an average 'symmetric percent volume change' (SPVC, as defined in[61]) of less than 0.01.

Phase 2, Subaim 1.3 Add future timepoint prediction functionality to the pipeline

Future timepoint predictions will be achieved by leveraging the work of close collaborators[64],[65] who have demonstrated that: 1) external factors, including the subject's genotype and health factors, have a significant impact on the subject's anatomy as observed by MRI and 2) a collection of patients can help identify complex spatial pathology in a new unseen individual patient. They employ a generative Bayesian formulation that uses a linear mixed effects model (LMM)[66] to learn model parameters and a least squares kernel machine (LSKM) regression model[67] to perform predictions.

The model has been used to predict subject neuromorphometrics from genetic, clinical and imaging data from the ADNI longitudinal study[68]. This dataset contains 2 to 10 follow up-scans acquired 0.7 to 7 years after baseline. The model parameters include 21 genetic loci associated with AD as well as standard clinical factors including age, gender, marital status, education, disease diagnostic at baseline, and cognitive test scores at baseline. Model parameters are learned from 341 randomly chosen subjects and predictions have been evaluated on a separate set of 100 subjects.

We expect this subaim to take one research fellow 640 hours to complete (50% time for 4 month)

The criteria for success for this subaim will mirror that of the phase I feasibility study and our 510k validation plan: An average Dice score greater than 0.8 across subcortical regions. Since timepoint ordering reversal is not applicable to future timepoint prediction, the 'symmetric percent volume change' (SPVC) criteria will not be applied to this subaim.

Phase 2, Aim 2: Integrate the longitudinal pipeline with the AutoRegister tool

AutoRegister is another product CorticoMetrics is developing with plans to market as a software only medical device. It is a tool to set the imaging coordinates of an MRI acquisition, a process commonly referred to as *slice prescription*. AutoRegister and its longitudinal use case is further described in section B.2.3. Here we describe our forward-looking plans to integrate these 2 products. The MGH subcontract on this grant and subsequent master research agreement with Siemens will critical to the success of the Aim. These relationships are further described in the Commercialization Plan and Letters of Support.

Phase 2, Subaim 2.1. Add longitudinal use case functionality to AutoRegister device

In AutoRegister's typical use case, it searches for a baseline session when a patient is registered for an MRI. It then retrieves this imaging data which is uses to compute an FOV and send to the console.

Here we add support for the longitudinal use case. In addition to retrieving the baseline session, when integrated with this product, AutoRegister will search for and retrieve all potential longitudinal timepoints as well. The device in this proposal will compute the "midspace" FOV that maximizes statistical power across these timepoints and AutoRegister will transmit these coordinates back to the console.

Phase 2, Subaim 2.2. Add longitudinal semantics to data generated by AutoRegister

The full longitudinal processing stream involves running the cross-sectional stream on each timepoint, computing the midspace FOV, then re-processing each timepoint with additional longitudinal information. Adding longitudinal semantics to the data that has been acquired using AutoRegister will allow us to skip certain steps in this processing pipeline, which will improve processing time and prepare the device for the demands of clinical use cases.

Phase 2, Subaim 2.3. Use AutoRegister to prescribe scans for hippocampal subregion segmentation.

FreeSurfer can currently generate hippocampal subfield segmentations using standard MRI inputs (1mm isotropic multi-echo MPRAGE). At these resolutions, however, the segmentation is largely driven by the prior probabilities of the atlas and is thus insensitive to many disease effects[52]. To achieve optimal subfield segmentations, a higher-resolution image of the hippocampus is required. A high resolution T2-weighted sequence has recently been gaining popularity amongst researchers to image and classify hippocampal

subfields[69],[70],[71],[72]. This sequence has a limited FOV and has slices aligned perpendicularly to the long axis of the hippocampus. Acquiring quality hippocampal data using this sequence requires a highly trained MRI technician as extensive experience is required to accurately place the FOV. This has limited the technique to research settings. CorticoMetrics' complementary product offering, AutoRegister, has been designed to solve exactly this type of problem. In this aim we will augment AutoRegister's existing slice prescription capabilities with the ability to prescribe high-resolution hippocampal and amygdalar scans. We will compare AutoRegister's performance to experienced MRI technicians who have no prior experience with this technique.

Phase 2, Aim 3: Submit for FDA 510(k) clearance

In this penultimate aim of the proposal, we curate the work accomplished to date to prepare and submit a 510(k) application. We do this by drafting additional regulatory documents, by following CorticoMetrics' QMS to review and revise these documents and preparing the 510(k) submission package.

Phase 2, Subaim 3.1: Draft remaining documents required by CFR 820.30(c)

Verification Plan: We will adhere to our QMS, which is based off IEC 62304 guidelines, to develop our verification plan. Specifically, we will adhere to sections 5.5.1, 5.5.2, 5.5.3, and 5.5.5. Since we will be filing as a Class B device, section 5.5.4 does not apply. Deliverables from Phase I, aim 1.3 will serve as an initial draft and working implementation of the verification plan. To iterate on the verification plan, CorticoMetrics will follow its SOPs as defined by its QMS, including design review procedures, as well as regular interactions with our regulatory advisors.

Validation Plan: We will adhere to our QMS, which is based on IEC 62304 guidelines, to develop our validation plan. Deliverables from Phase I aim 3, as well as pass/fail criteria (Dice > 0.8; SPVC < 0.01) will serve as an initial draft and working implementation of the validation plan, which uses peer-reviewed methodology across a variety of datasets[25]. CorticoMertics will iterate on the verification plan as defined by our QMS and under the guidance of our regulatory advisors. While not essential for regulatory validation, commercial validation is an equally important prerequisite to a successful product. Plans for two initial pilot projects to demonstrate use cases and ROI have been developed and is further described in the commercialization plan. Additionally, we will follow our QMS and advisors to draft the risk management and human factors and usability plans.

Phase 2, Subaim 3.2: Perform design reviews and make resulting changes

To iterate on these documents, CorticoMetrics will follow its SOPs as defined by its QMS, including design review procedures, as well as regular interactions with our regulatory advisors. Reviews and changes will be logged in CorticoMetrics' QMS and the device's design history file (DHF)

Phase 2, Subaim 3.3: Execute Validation and Usability plans and submit for FDA 510(k) approval

We conclude the project by working closely with our regulatory advisors to prepare and submit a 510(k) application. CorticoMetrics has met with the FDA on June 4th, 2018 to discuss our submission strategy for our initial 510(k) submission: a clinical translation of FreeSurfer's cross-sectional stream. Since the science, technology, and validation techniques are nearly identical, CorticoMetrics does not believe a pre-submission meeting is required for this submission.

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Commercialization Plan

Value, Expected Outcomes and Impact

Background

Neurodegenerative disease is an encompassing term for a set of over 600 diseases in which the nervous system progressively and irreversibly deteriorates. Alzheimer's disease (AD), the most prevalent of the neurodegenerative diseases, affects approximately 15 million people worldwide[1]. Estimates expect the incident rate to triple in America[2] and Europe[3] by 2050.

The FDA has recently released a draft guidance document for the development of drugs to treat early Alzheimer's disease[4] which states that a *biomarker* alone is a sufficient endpoint for a successful clinical trial. This is a prominent departure from previous guidelines which required that a drug also demonstrate a clinical improvement. A *biomarker* is a reliable way to determine the medical state of a patient[5]. The biomarker market is expected to exceed [redacted] by 2021[12].

MR neuromorphometry is the process of measuring the dimensions of various structures of the brain from MRI images. Some examples of *neuromorphometrics* include ventricular shape, hippocampal volume and cortical thickness. *MR Neuromorphometrics* are promising candidates for *biomarkers*.

A *longitudinal study* is an investigation where repeated measures are collected at multiple timepoints. Unlike a more conventional (cross-sectional) study that assumes all collected measures are independent, a longitudinal study will exhibit strong correlations between repeated measures. This requires special statistical techniques to ensure valid and unbiased results. Performed correctly however, these techniques can exploit the correlations within the repeated measures and generate additional statistical power compared to cross-sectional methods. This increase in statistical power translates in an improved ability to detect subtle changes at the individual level and a reduction in clinical trial sample sizes.

A major pain point in current *longitudinal neuroradiology workflows* is the time radiologists spend manually aligning the most recently acquired imaging data to the baseline so that an accurate assessment of change can be made. This severely impacts radiology report turnaround times (RTAT).

In the research community, *longitudinal MR neuromorphometrics* (repeated measures of the changes in the shape and sizes of various brain structures, as measured by MRI) have been shown to be extremely effective *imaging biomarkers* for the assessment of various *neurodegenerative diseases* including Alzheimer's disease[6], and MCI (mild cognitive impairment; considered to be an early stage of evolving Alzheimer's disease[7, 8]). These metrics have been found to be stable in both inter-session and inter-sequence test-retest paradigms[9].

FreeSurfer is the leading software package in the research community to automatically generate *MR neuromorphometrics* from MRI data. It is in use by over 32,000 researchers worldwide. FreeSurfer's existing

longitudinal analysis stream has become one of the main tools used for analyzing the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset, and has resulted in a better understanding of the time-course of *neuromorphological* changes early in the disease[10, 11]. It has also been a main tool for understanding the extensive cortical changes that occur in Huntington's Disease and has resulted in a paradigm shift in how that disorder is conceived[12, 13]. We have demonstrated that FreeSurfer's *longitudinal neuromorphometric* analysis of ADNI data results in about **a 4-fold improvement in discrimination** relative to what is afforded using more conventional cross-sectional approaches.

Proposal

CorticoMetrics is currently translating FreeSurfer into a clinical tool to automatically generate neuromorphometry reports from MRI imaging data. An initial prototype of this neuromorphometry report is appended to the end of this document. We expect to file our first 510(k) submission for our class II software-only medical device in the fall of 2018 (predicate: K170981). **The goal of this proposal is to augment our device with longitudinal neuromorphometric analysis capabilities** by translating, and seeking 510(k) approval for, FreeSurfer's longitudinal analysis stream.

Impact

A clinical device capable of automatically generating longitudinal neuromorphometric reports will increase the quality of patient care. Integrating this proposed device with AutoRegister, another device under development at corticometricis, will alleviate the pain point in current longitudinal neuroradiology workflows of manually aligning recent imaging data to baseline. This has the potential to drastically reduce longitudinal neuroradiology report turnaround times.

Our unbiased statistical methods will increase the power available to clinical trials affording the detection of more subtle changes or alternatively the enrolment of fewer subjects.

Quantitative imaging at a massive scale coupled with modern approaches to "big data" could revolutionize the understanding of neurodegenerative diseases and human biology more generally.

Company

Vision

CorticoMetrics believes that the **future of healthcare** lies at the intersection of **personalized medicine** and **machine intelligence for decision support**. We are well positioned with expert domain knowledge and working collaborations in both these areas and are passionate about revolutionizing the field of medicine. With deep and longstanding connections to the neuroimaging research community, CorticoMetrics understands that clinical care is at least 2 decades behind the research community. We have made it our business to remedy this.

History

CorticoMetrics was co-founded by Dr. Bruce Fischl and Mr. Nick Schmansky in 2012. Dr. Fischl has devoted his career to advancing the state of neuroimaging research. He co-developed FreeSurfer, an open-source software package currently licensed to more than 32,000 clinicians and neuroscientists. Hundreds of papers have been published using results from FreeSurfer that have led to deeper understandings of dozens of neurologic conditions and disorders.

[redacted] Mr. Schmansky had been FreeSurfer's lead software engineer for 10 years. Having worked as a software engineer in industry and scientific research for over 20 years, was determined to fulfill a long-held dream: starting a company to improve the lives of people through innovative healthcare. This confluence of events resulted in the creation of CorticoMetrics in 2012, and the ensuing award of the first NIH STTR grant in October 2013. Karen J. Roberts, Ph.D., joined CorticoMetrics in 2013 to advise on business matters. Her areas of expertise include operations, finance, technology, project / program management, and legal. She received a Ph.D. from Boston University and an MBA (Entrepreneurial Studies) from Babson College - Franklin W. Olin Graduate School of Business.

Status

Today, CorticoMetrics employs 4 full-time employees. Dr. Wighton joined the company in November 2015, and has assumed the role of lead software engineer. He is co-PI on this application and AutoRegister, a funded STTR proposal with mutually beneficial points of integration with this proposal. Mr Sang Lee joined the company in April 2016, bringing with him experience in project management and clinical trial management and assuming the role of regulatory lead. Mr Lee Tirrell joined the team in June 2017, brining hands on experience with the FreeSurfer software and software QA experience.

To date, CorticoMetrics has secured approximately 5 million dollars in funding from the NIH. Working closely with regulatory consultants, we have created a quality management system (QMS), drafted standard operating procedures (SOPs), identified modern technologies and developed a cloud-based infrastructure harmonized with IEC 62304 so that all current and future work will be FDA 21 CFR 820 compliant.

CorticoMetrics' first product, THINQ, automatically generates neuromorphometry reports from MRI data. It is currently under active development and we expect to file for 510(k) pre-market approval as a class II software only medical device in the fall of 2018. An example neuromorphometry report that THINQ generates is appended to the end of this document. Our second planned commercial offering, AutoRegister, automates and personalizes the process of entering imaging acquisition coordinates (FOV), ensuring reliable and comparable images and reducing radiology report turnaround times (RTAT).

Strategy

At RSNA 2017, CorticoMetrics announced a signed distribution deal with EnvoyAI to integrate our initial product, THNIQ, into the EnvoyAI platform. Also at RSNA 2017, TeraRecon announced a distribution partnership with EnvoyAI to sell and market the EnvoyAI platform. TeraRecon is the largest independent, vendor neutral medical image viewing solution provider with a focus on advanced image processing innovation.

CorticoMetrics plans to leverage partnerships like this to distribute our products and generate revenue. Once we have established an initial revenue stream, however small, we intend to seek private investment, possibly in conjunction with a Phase IIB application to fund operations not possible to fund under this granting mechanism (i.e business development, sales & marketing, executive management, regulatory activities, and production and support)

Markets, Customers, and Competition

Markets

There are 2 major market segments we are targeting with this device: the clinical market and the drug development market.

Clinical Market

The primary stakeholder in this market segment is the radiologist viewing structural MR neuroimaging data and completing a radiology report. Currently, a radiologist must spend an inordinate amount of time manually aligning the most recent imaging volumes to baseline so that a meaningful comparison can be made. The radiologist also does not have an objective means of determining when the images are in alignment, nor do they have objective metrics for quantifying changes across images. After purchasing the tool described in this proposal, the radiologist will have access to quantitative neuromorphometry data in a PDF document to consult while drafting the radiology report. Additionally, imaging data across timepoints will already be in alignment when arriving at the radiologist's workstation with no intervention in workflow from the radiologist's perspective. This tool will dramatically reduce report turnaround times (RTAT), increase confidence in the radiologists' assessment and improve the quality of clinical care.

While the market for quantitative imaging is relatively small (estimate predict it will be between [redacted] by 2021[14]), CorticoMetrics believes this market has to potential to grow exponentially over the next decade as the demand for objective "radiomics" increases and the technical and logistical barriers to sophisticated image processing pipelines and compute resources are removed. CorticoMetrics is positioning itself to be a leader in this emerging market.

The proposed device will also alleviate the burden due to head displacement confounds. There are three types of head displacement confounds in MR neuroimaging: 1) Inter-session displacement 2) Intra-session displacement and 3) Intra-sequence displacement. A recent study on the economic burden of intra-sequence displacement alone has estimated to cost hospitals [redacted] per MRI scanner per year[15]. If we assume an MRI density 36.72/million in the US[16], then the **total US healthcare burden due to intra-sequence MRI**

displacement is [redacted]/year. The proposed device, as well as AutoRegister, a complementary product under development at CorticoMetrics which has natural points of integration with this proposal (see Research Plan for further details), is designed to comprehensively address and remove all 3 types of head displacement confounds.

Drug Development Market

In this market segment, the clinical trial investigator is the primary stakeholder. After purchasing the proposed device, they will have an easy way to automatically generate *neuromorphometrics* from MR imaging data to replace the time-consuming task manual process. Additionally, the increased power realized by using our unbiased longitudinal methods, will enable them to either detect smaller changes or reduce the required sample sizes of their studies.

The proposed device would be applicable to any clinical trial involving an MRI *neuromorphometric* endpoint. The global Alzheimer's drugs market *alone* stood at an overall valuation of [redacted] in the year 2017. This valuation is estimated to reach to a figure of [redacted] by the end of 2025[17]. As FDA clearance is not required to enter this market, it could serve as one possible source of revenue in Phase III. (See the section 'revenue stream' for further details)

Competition

There are 3 FDA cleared neuromorphometry reporting devices: NeuroQuant, Icobrain and NeuroReader. All 3 devices have been cleared as Class II software only medical devices (product code: LLZ)

NeuroQuant

NeuroQuant (K061855/K170981) was the first MR neuromorphometry reporting device to receive FDA clearance in 2006. Their validation plan submitted to the FDA relies heavily on reference data generated from FreeSurfer: the source from which CorticoMetrics' technology is derived. NeuroQuant automatically generates several reports containing various volumetric subcortical metrics and associated normative ranges, stratified by use case. In September 2017, they received approval to augment their device with longitudinal reporting functionality.

NeuroReader

NeuroReader (K140828) was FDA cleared in February 2015. Unlike NeuroQuant and IcoBrain, NeuroReader only offers a single neuromorphometry report containing volumetric subcortical metrics and associated normative ranges. NeuroReader does not currently offer longitudinal reporting functionality.

Icobrain

Icobrain (K161148) was FDA cleared in August 2016. Like neuroquant, they offer a variety of reports stratified by use case which contain a selection of volumetric subcortical metrics and associated normative ranges. They also offer longitudinal reporting functionality.

CorticoMetrics' Competitive Advantage

CorticoMetrics considers our proposed device to be substantially equivalent to both NeuroQuant and IcoBrain. We too intend to deliver a neuromorphometry report with associated normative data and support for longitudinal analysis. We believe, however, that our product will have 2 notable advantages over the competition. First, in addition to providing the subcortical volumetrics with normative ranges, as our competitors do, we will also provide various metrics of cortical thickness with normative ranges. **Our product will be the only one on the market capable of performing longitudinal analysis of surface based neuromorphometrics**. Also, a considerable amount of research has been invested into our longitudinal stream to ensure that it is unbiased (see Research Plan Section B.2.2 for details). There are not sufficient details on our competitors' methodology to assess which biases their streams may be subjected to. To objectively evaluate our competitive advantage in this area, we will curate a small dataset to test for the presence of these biases (see [18] for details) and submit them to our competitors for analysis. Additionally, integrations with another offering under development at CorticoMetrics (AutoRegister) will ensure that imaging data across timepoints will be in alignment before being viewed by the radiologist. This will help significantly decrease report turnaround times (RTAT).

Strategic Partners

CorticoMetrics has forged partnerships with 3 key companies as we design, develop, evaluate and deploy our products: Massachusetts General Hospital (MGH), Siemens Healthcare USA and EnvoyAI. These relationships are further described in the attached Letters of support.

Massachusetts General Hospital

As one of the world's leading hospitals, some of the key thought leaders in the field of radiology reside at MGH and have considerable influence over which direction the field will move. CorticoMetrics has been working closely with two MGH neuroradiologists for several years. Drs. Steven Stufflebeam and Otto Rapalino have been our two most enthusiastic champions throughout MGH community and neuroradiology community more broadly.

CorticoMetrics has also forged a relationship with the newly formed MGH Center for Clinical Data Sciences (CCDS) to help deploy, test and optimize our products (see letter of support from the CCDS Director Mark Michalski, and budget support for the lead CCDS engineer, Sean Doyle). The ongoing collaboration between the CCDS and CorticoMetrics provides the ideal venue to showcase our products, gain practical integration experience and get critical feedback on usability and design from clinicians directly engaged in detecting change and assessing disease effects.

Siemens Healthcare USA

MGH Martinos Center is a sub-contract on this grant, led by Dr. Bruce Fischl. The MGH Martinos Center and Siemens Medical Solutions, USA pursues an active and dedicated Academic-Industrial partnerships under a master research agreement (MRA). The MRA allows certain Martinos employees access to considerable confidential details and technical specifications of the Siemens MR System. Additionally, Siemens supports 4 full-time site scientists co-located at the Martinos center to support collaborative projects. While CorticoMetrics is not party to this MRA and therefore not allowed direct access, this relationship is nevertheless extremely valuable to understanding industry trends and subtle technical nuances. This relationship will be critical to the

integration with the AutoRegister project, as described in the Research Plan. CorticoMetrics has begun exploring how to forge its own independent agreement with Siemens.

EnvoyAI

EnvoyAI is simplifying access to AI algorithms for physicians by providing integration into existing workflows, starting with the TeraRecon product suite. The company's products include a free developer platform, an open API, and a local virtual appliance designed to streamline the clinical implementation of trained machine learning algorithms. The EnvoyAI platform allows hospitals to quickly integrate a growing catalog of algorithms seamlessly into their workflow, while supporting both cloud and local deployment configurations. CorticoMetrics and EnvoyAI announced their distribution deal at RSNA 2017[19].

Intellectual Property (IP) Protection

CorticoMetrics does not currently hold, nor plan to submit, patent claims on any of its current or proposed technology. The FreeSurfer code is not subject to any patent claims, and is licensed under a 'BSD/MIT-like' open-source license, where the software is free to use for commercial use, and does contain 'viral' provisions (i.e. those found in the GNU license).

CorticoMetrics is often asked about the danger of working with open-source code, where conceivably a competitor could 'take' the FreeSurfer functionality and incorporate into their own product. In principle this is true, but in practice is impractical, as neuroimage processing pipelines are quite complex, and algorithm (and its coding) expertise must be internal to the company. Each competitor has their own scientists and engineers who 'own' and maintain the algorithms they have selected (those not based on FreeSurfer). CorticoMetrics has the distinct advantage of having as co-founders the primary algorithm developer (Dr. Bruce Fischl) and software engineer (Mr. Nick Schmansky) of the FreeSurfer software package.

Finance Plan

In early 2017, CorticoMetrics participated in the NIH 'Commercialization Accelerator Program' (NIH-CAP), for selected Phase II awardees. Mr. Nick Schmansky and Mr. Sang Lee received training in necessary Phase III activities, culminating in a presentation of proposed product offerings to a 'shark-tank'-like committee. Valuable feedback was received and highlighted the need to establish a strong product differentiator from competitors, the necessity of establishing industry contacts well-before Phase II completion, and the need to achieve a concrete 'milestone' (ie. 510(k) clearance) prior to approaching investors.

Mr. Nick Schmansky and Mr. Sang Lee have also participated in several events sponsored by a Boston-area organization called 'The Capital Network', which provides fundraising education for startups. The events have provided instruction on funding approaches, as well as one-on-one meetings with Angel and VC investors. Several informal contacts with local investors were established. More recently, Dr. Wighton submitted our complementary product (AutoRegister) to NCI's Investor Initiatives Program to seek investor funding and additional strategic partners.

CorticoMetrics recognizes the critical importance of the Phase III stage. While we are confident we can secure 510(k) approval, and equally confident of an immediate revenue stream after approval through our distribution deal with EnvoyAI, we will lack the funds to properly scale operations post-approval. CorticoMetrics believes that private investor funds are critical to accelerate and successfully commercialize our products. Once a proof-of-principle revenue stream has been established, we intend to seek private funding, possibly in conjunction with a phase IIB bridge application, to build out the following areas: business development, sales & marketing, executive management, regulatory activities, and production and support.

Production and Marketing Plan

Production costs of software are generally realized in the following areas: sales support, tech support, advertising, packaging and distribution, licensing agreements, liability insurance, sales processing and periodic product updates. Additionally, the FDA requires medical device manufacturers involved in the distribution of devices (including software devices) to follow certain requirements and regulations once devices are on the market. These include such things as tracking systems, reporting of device malfunctions, and registering the establishments where devices are produced or distributed. Postmarket requirements also include postmarket surveillance studies. Currently, the CorticoMetrics team has the skills and resources necessary to address these activities sufficiently for a first product sale. However, investor funding will be necessary to fully address the capital and personnel needs to achieve successful commercial growth.

CorticoMetrics is bringing its initial neuromorphetry reporting device, THINQ, to clinical markets in Fall 2018 (these efforts are outside the scope of this proposal; the incorporation of the functionality proposed in this project will happen at a later date). Introduction of our products has already begun through collaborations at MGH and an initial prototype of THINQ has already been integrated into EnvoyAI's platform for testing and non-clinical use. We are currently seeking to establish pilot projects to develop case studies and return on investment (ROI) stories to support further marketing of the product. We have planned two initial case studies for the proposed project. The first case study involves crafting a dataset specifically designed to look for methodological biases. We will then run this dataset through our product as well as our competitors to demonstrate our ability to generate more statistical power. The second case study involves measuring radiology report turnaround times (RTAT) before and after integrating the proposed product into a radiology workflow.

We will expand marketing efforts to a larger base of prospects through trade show attendance and training events and leveraging CorticoMetrics' extensive network of neurology clinicians and researchers, both in the northeast and nationally, to identify and build out sales channels. We will also market professional services to the existing base of 30,000+ FreeSurfer users. CorticoMetrics has begun working with the global medical imaging field through interactions with open-source developers and individuals at the Radiological Society of North America (RSNA) annual conferences to discuss new standards in quantitative medical imaging. CorticoMetrics has begun discussion with the Quantitative Imaging Biomarker Association (QIBA) for the creation of a committee on quantitative structural MRI biomarkers, positioning CorticoMetrics to pave the pathway for this standard in clinical imaging.

We anticipate that additional funding will be needed for the hiring of sales and support staff to undertake the commercialization of the technology, and to support the sales efforts that potential channels have with their existing and prospective end users to target both advanced visualization capabilities and quantitative biomarker capabilities of CorticoMetrics tools. Additional funding will also be required for the support of acquired customers.

Revenue Stream

Once the proposed device obtains 510(k) approval, a revenue stream becomes instantly available through the already established distribution deal with EnvoyAI. CorticoMetrics expects to have several additional distribution deals established by the end of this proposed project. CorticoMetrics is currently exploring efficient means to bring our product to the clinical trial/cro market to serve as an additional revenue stream.

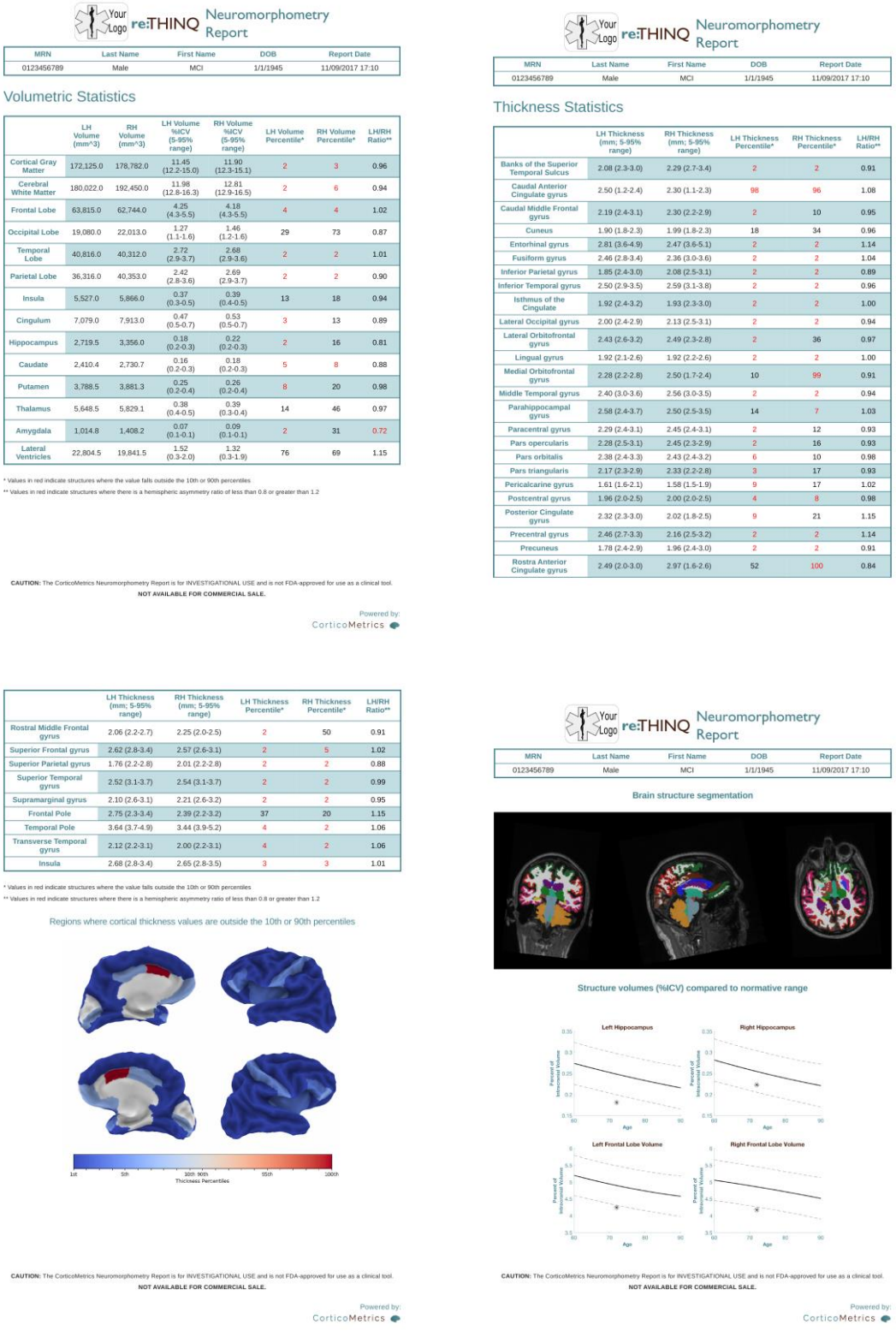

Figure 1: Sample neuromorphometry report automatically generated from MRI data by CorticoMetrics initial product, THINQ. Here, we propose to augment THINQ with longitudinal analysis functionality. We expect to file 510(k) submission for THINQ in Fall 2018.

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LEADERSHIP PLAN

The project 'Unbiased longitudinal neuromorphometry for clinical decision support' will be a Multiple PD/PI application. Dr. Paul Wighton of CorticoMetrics LLC, will serve as contact PI and will be responsible for submission of progress reports to the NIH and all communication. Dr. Bruce Fischl, of Massachusetts General Hospital (MGH) will also serve as PI.

Dr. Wighton has worked as a Postdoctoral Research Fellow at MGH, within the A.A. Martinos Center for Biomedical Imaging, in development of real-time fMRI techniques, under the supervision of Dr. Andre van der Kouwe, and as a Staff Scientist at CorticoMetrics. In this project, Dr. Wighton as PI will primarily be responsible for the engineering aspects, and Dr. Fischl PI will primarily be responsible for the scientific aspects.

The PIs will be in close contact and constant communication by proximity of CorticoMetrics' location to the lab space of Dr. Fischl at MGH in [redacted].

The PIs have had a good working relationship at MGH and CorticoMetrics, where no conflicts have arisen. However, if a potential conflict develops, the PIs shall meet and attempt to resolve the dispute. If they fail to resolve the dispute, the disagreement shall be referred to Dr. Andre van der Kouwe of MGH for arbitration. Dr. Kouwe is well known to both PIs over the course of working together for several years at MGH, and is trusted to resolve any potential conflict.

INTRODUCTION

We thank the reviewers of our initial submission for their detailed and constructive feedback, which we believe has substantially improved the quality of this re-submission. We also thank the reviewers for acknowledging that the "project is scientifically rigorous with carefully worked out details on how the aims are going to be achieved." and that "as for [sic] as commercialization is concerned, the approach is well defined and thus rigorous."

To facilitate the review, changes to the Research Plan for this resubmission have been highlighted in yellow.

The most substantial criticisms of the initial submission were that "the timeline of such a developmental process seems excessive" and that "innovation is limited to the propose [sic] image processing pipeline which is not innovative in the image processing software development community". We address both these concerns by adding additional functionality to our longitudinal pipeline. In this re-submission, we propose to augment the initial proposal with functionality to segment hippocampal subfields and amygdalar nuclei. We also propose to extend the pipeline functionality to perform predictions at arbitrary times in the future.

The hippocampus and amygdala consist of several distinct regions, known as *subfields* (hippocampus) and *nuclei* (amygdala), that are affected differently by AD. These have been traditionally treated as a single structure under MRI, however recent advances in high-resolution MR imaging have made it possible to study hippocampal and amygdalar subfields *in vivo*. No commercial package, and in fact no other research package, enables labeling of these structures even cross-sectionally, while here we propose to add both cross-sectional and explicitly longitudinal analysis tools to our capabilities. The addition of these features will provide clinicians with a richer set of potential AD biomarkers and further inform the understanding of the progression of AD. Information from the subfields and nuclei have been shown to improve on the ability to diagnose AD, and further, incorporating explicit longitudinal modeling into the segmentation allows the differentiation of early MCI from both controls and AD subjects, a critical distinction that could not be detected using cross-sectional methods.

It is widely believed that the onset of the underlying pathology for AD begins years, if not decades, prior to the appearance of clinical symptoms. While a cure for AD remains elusive, any intervention that could delay disease onset or progression would represent a significant alleviation of its healthcare burden. A method to predict the onset of AD would therefore be a valuable tool in the clinician's arsenal. While predicting future changes in neuromorphometry alone may not be sufficient for a reliable AD predictor, it may serve as one of several critical components or further understand the underlying mechanisms of AD and inform early diagnosis. We also add that some early amyloid clearance trials have shown some beneficial effects, and that there are several ongoing clinical trials looking at both amyloid and tau. Enormous efforts in the pharmaceutical industry have focused on AD, and the tools we propose would thus be perfectly positioned to provide quantitative surrogate biomarkers that would be critical capabilities for this endeavor.

Another critique of the initial submission was that a "clearly defined pass-fail metric would have strengthened the rigor". Since the initial submission we have met with the FDA to discuss our 510k strategy for our initial submission: a cross-sectional neuromophemetry reporting tool. We have drafted a validation plan based on feedback received from this meeting (Dice > 0.8 when compared with expertly labeled dataset) and will use this criteria for the longitudinal stream as well. We also adopt an additional, previously published, criteria for the longitudinal steam (symmetric percent volume change; SPVC < 0.01) to ensure no timepoint ordering bias is present.

Finally, we end with two final points. First, while it is true that “It is not clear if imaging and imaging alone can provide such a biomarker”, quantitative surrogate biomarkers are still of enormous potential value to clinicians and researchers searching for cures to devastating diseases such as Alzheimer’s. They would add quantitative automated information with the potential to detect the effects of disease-modifying therapies early in the course of a clinical trial, making the entire process more rapid, efficient and cost-effective, while also giving clinicians large amounts of additional information that has been shown to be important for diagnosis. Second, while it is also true that we are mainly proposing to port and integrate existing algorithms to a clinical platform, we stress that the innovation in our proposal stems from the overall functionality that would be available to clinicians and pharmaceutical companies at the successful completion of our project – a complete end-to-end system that acquires optimal data at each time point and across time, then processes this data in an unbiased and powerful manner designed to extract clinically relevant information. No such system exists today.

RESOURCE SHARING PLAN

In the proposed project, previously curated publicly available datasets will be used to validate our work. Data and methodology used go generate the Phase I and Phase II validation studies described in the Research Plan will be archived. Under the Small Business Act, STTR grantees may withhold their data for 4 years after the end of the award for business development reasons. CorticoMetrics, however, is engaged in several campaigns to promote the interoperability of FreeSurfer: the leading software for package for generating MRI neuromorphometrics that is freely available. See https://github.com/corticometrics for details. We will also publish our statistics that were derived from these data as well as descriptive information regarding the demographic distribution, scanner type, and field strength of the data.

FACILITIES & OTHER RESOURCES

Project/Performance Site Primary Location

The proposed project ‘Unbiased longitudinal neuromorphometry for clinical decision support' does not require special equipment or facilities, other than off-the-shelf PC workstations, which exist on-site at the primary site location (CorticoMetrics), at Location '1' (CorticoMetrics rented office space) and at the MGH site (Location 2).

Project/Performance Site Location 1

CorticoMetrics rents office space through WeWork at [redacted]

Project/Performance Site Location 2

The following is the facilities and resource description describing the 'MGH' site:

Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital

The imaging facilities of the Athinoula A. Martinos Center for Biomedical Imaging at the Massachusetts General Hospital are located on the Hospital’s Research Campus in the [redacted]. Additional imaging laboratories are located on the MGH Main Campus in Boston. The Martinos Center is closely affiliated with the Harvard-MIT Division of Health Sciences and Technology (HST) and the Harvard Center for Brain Science Imaging Facility, located in [redacted] Satellite research facilities are located at the Martinos Imaging Center at MIT.

The Martinos Center currently occupies ~85,000 ft^2 of space in the [redacted] and comprises basic and clinical research laboratories as well as educational areas and administrative offices.

INSTRUMENTATION AND LABORATORY DESCRIPTIONS

MRI Facilities

Large Bore (Human/Clinical) MR Systems

1.5T MRI Laboratory (Bay 2). This is a 1.5 Tesla Siemens Avanto 32-channel “TIM” system that has been upgraded to accommodate 96 RF receive channels. It uses a 60 cm whole-body MRI system capable of EPI functional imaging at a sustained rate of 15 images per second, CINE, MR angiography, diffusion and perfusion studies and spectroscopy. The system has a gradient strength of 45 mT/m and slew rate of 200 T/m/s, provides routine second-order shimming and has 32 independent RF receive channels for phased array coils, including a Siemens 32-channel head coil. Bay 2 also contains an assortment of audio, visual, and sensory stimulus equipment for fMRI studies including front and rear projection, audio stimulation, a subject response device and eye tracking setup. Stimuli can trigger or be triggered by the scanner. The stimulus equipment can be run using either of the PC or Macintosh computers installed and available for use in the Bay; alternatively, the user may operate the stimulus equipment from a personal laptop computer. Bay 2 is also equipped with a Siemens Syngo workstation for 3D image processing, cardiac evaluation, and quantitative image analysis.

3T MRI Laboratories. The Center currently has three 3 Tesla MRI systems, each described below.

3T MRI 1 (bay 3). This is a 32-channel Siemens Tim Trio 3T whole-body MRI scanner with an insertable 36 cm (gradient coil ID) head-only gradient. The whole-body gradient system uses the same gradients as the 1.5 T Avanto (45 mT/m strength, 200T/m/s slew rate). It has 32 independent RF receive channels for phased array coils, including a Siemens 32-channel head coil and a home-built 32-channel head coil for the gradient insert. The system is capable of EPI, second-order shimming, CINE, MR angiography, diffusion and perfusion studies, and spectroscopy. The asymmetric head gradient coil is capable of 60 mT/m and slew rates in excess of 600 T/m/s at a duty cycle of 70%, allowing single-shot 3mm resolution EPI with an echo spacing of 300 μs at a sustained rate of 14 images/second. Bay 3 also

contains an assortment of audio, visual, and sensory stimulus equipment for fMRI studies including rear projection, audio stimulation, subject response device, and eye tracking setup.

3T MRI 2 (bay 4). This is a 3T Siemens TIM Trio 60 cm (RF coil ID) 32-channel whole-body MRI with EPI, second-order shimming, CINE, MR angiography, diffusion, perfusion, and spectroscopy capabilities for both neuro and body applications. This system uses the same gradients as the 1.5 T Avanto (Bay 2; 45 mT/m strength, 200T/m/s slew rate). The system is equipped with the standard "TIM" 32 RF channel receivers, accommodating up to 32 element array coils (and has the Siemens 32-channel head coil) but has been specially upgraded to accommodated 128 RF channels. An upgrade to perform multinuclear imaging and spectroscopy has recently been installed. Bay 4 also contains an assortment of audio, visual, and sensory stimulus equipment for fMRI studies including rear projection, audio stimulation, subject response device, and eye tracking setup.

3T MRI 3 (bay 8*).* A new Siemens Skyra platform 3T MRI system was installed in 2010. The system comes with 64 RF channels, 40mT/m gradients and a 70cm patient bore for improved subject comfort and stimulus access. The system will provide capability for EPI functional imaging at a sustained rate of 15 images per second, CINE, MR angiography, diffusion and perfusion studies and spectroscopy. Bay 8 also contains an assortment of audio, visual, and sensory stimulus equipment for fMRI studies including rear projection, audio stimulation, subject response device. Stimuli can trigger or be triggered by the scanner. The stimulus equipment can be run using either of the PC or Macintosh computers installed and available for use in the Bay; alternatively, the user may operate the stimulus equipment from a personal laptop computer. This system is dedicated to connectomics imaging, in support of the multi-site Human Connectome Project consortium.

7T MRI Laboratory (bay 5). This is a unique ultrahigh-field 7.0 T head-only MRI with 80mT/m head gradient set, an Avanto whole-body gradient set, and 32 RF receive channels. The 7.0 T 90 cm (magnet ID) whole-body magnet was built by Magnex Scientific (Oxford, UK); the conventional MRI console, gradient and gradient drivers, as well as patient table were provided by Siemens. The system is shielded by a 460-ton steel shield. Integration of these components and the design and construction of RF coils were performed jointly by MGH and Siemens personnel. The 7T whole-body magnet is augmented by a 80mT/m, 800 T/m/s slew rate head gradient set (Siemens) for echo planar imaging and second-order resistive shim coils under computer control. With its high-performance gradient set, the system can provide better than 100-μm resolution and ultra-fast EPI readouts for reduced image distortion. The system uses a home-built 32 channel or 8 channel head array coil. Recently the system has been upgrade by Siemens to contain 8 independent 1kW transmit channels capable of simultaneous parallel excitation with different RF pulse shapes for B1 shimming and/or parallel transmit methods such as transmit SENSE.

MEG/EEG Facilities

The MEG/EEG facility is equipped with a state-of-the-art 306-channel planar dc-SQUID Neuromag Vectorview MEG system that allows noninvasive spatiotemporal mapping of human brain activity. The Neuromag system, comprising 306 MEG channels (2 planar gradiometers and a magnetometer at each of 102 sites) and 128 EEG channels, located in an Imedco magnetically shielded room, with a shielding factor of approximately 250,000 at 1Hz. Computer-controlled visual, auditory, and somatosensory stimulation systems as well as behavioral response monitoring and eye movement tracking equipment are available in the laboratory. For data analysis we employ the MNE software package, which allows smooth integration of MEG, EEG, MRI, and fMRI data. In addition, the laboratory provides access to other proprietary and free academic analysis packages.

In addition to the MEG recording room, the MEG laboratory includes a second RF shielded room for EEG recording. Both rooms will have optical cables to enable simultaneous use of a 32-channel source/32-channel detector diffuse optical tomography (DOT) system with EEG or M/EEG recordings. The system is equipped for optical and psychophysiological recordings and for delivering and controlling sensory stimuli. All data are stored on a RAID storage system with terabytes of online storage capacity. The data are available over a high-bandwidth local network to all analysis computers (Linux, SGI, HP, and Sun workstations and servers, and our new supercomputer). Several advanced source localization methodologies implemented by a large group of biophysicists are available to users.

MR-PET Facilities

A new MR-PET suite was completed in August 2010. This state-of-the-art facility houses a full range of instrumentation for novel combined MR-PET imaging technology, including:

3T MR-PET scanner. The combined MR-PET system (Siemens Medical Solutions) consists of a 3T Siemens TIM Trio 60 cm (RF coil ID) 32-channel whole-body MRI with PET head camera insert for simultaneous MR-PET acquisitions. This system has EPI, second order shimming, CINE, MR angiography, diffusion, perfusion, and spectroscopy capabilities for both neuro and body applications. It uses the same gradients as the 1.5 T Avanto (Bay 2; 45 mT/m strength, 200T/m/s slew rate). The system is equipped with the standard "TIM" 32 RF channel receivers, accommodating up to 32 element array coils. Bay 6 also contains an assortment of audio, visual, and sensory stimulus equipment for fMRI studies including rear projection, audio stimulation, subject response device, and eye tracking setup. The system contains one of the first PET cameras capable of simultaneous PET acquisition during MR acquisition, and is located adjacent to the research cyclotron. The PET system is a head-only insert camera. A second MR-PET system (Siemens Medical Solutions) is anticipated for installation in 2011.

Cyclotron. A Siemens Eclipse HP self-shielded 11 MeV cyclotron with single-beam extraction and a four-position target changer (targets currently available: ^{11}C gas target, ^{18}F fluoride water target, ^{18}F F_2 gas target, $^{15}O_2$ target, $^{13}NH_3$ water/ethanol target).

Radiochemistry laboratory. Includes 2 full-sized hot cells and six mini hot cells for automated radiochemistry, a GMP-qualified nuclear pharmacy with an isolator hot cell and a class-100 biosafety cabinet. Several synthesis modules have been installed, including: Explora FDG4 Module, Explora GN Module for general nucleophilic substitution reactions, Explora GPC for ^{11}C-methyl iodide processes, Hydrogen Cyanide Module, and ^{15}O water module. In addition, a GE Fxn, and Fxc system was added in September 2010 to complete the radiochemistry facility.

Analytical chemistry laboratory and a blood analysis laboratory. Instrumentation in these laboratories includes automated gamma counter and multi-channel radioisotope analyzer.

Behavioral Testing Laboratory. The behavioral testing suite, located on the second floor of Building 149, provides a quiet and controlled environment for neuropsychological testing, developing and piloting behavioral paradigms, and running pre- and post-scan experiments with children and adults in human studies. It consists of two testing rooms with one-way mirrors (rooms 2236, 2234), separated by a control room (room 2235), which may also serve as an observation station or additional testing space. Each of these rooms is equipped with PC and Macintosh computers and a button-press response box (with millisecond accuracy). These response boxes are identical to those used in the MR research bays, allowing for portability of the paradigms developed in the behavioral setting. Auditory stimuli may be presented via speakers in sound-field or over headphones. A digital audio tape recorder, microphone, touch-screen monitor, video projector and projection screen are also available for stimulus presentation and/or recording subject responses. Transfer of experimental paradigms and data backup may be accomplished with removable media.

Mock Magnet. The mock magnet is used to acclimate normal and clinical populations (children and adults) to the MRI environment in preparation for participation in MRI studies. The mock scanner is modeled after the Siemens 3T Allegra system in both structure and dimensions. Its parts include an original Siemens patient table, funnel and head coil. Transducers and recordings of scanner noise from the Siemens 1.5T (Sonata) and 3T are used to simulate the vibrations and pulse sequence noises associated with the actual scanning experience. Stimuli may be presented using headphones or a rear projection system; a mirror is mounted on the head coil (as also found in Bays 2, 3 and 4), and a button box is available for responding to stimuli. Potential subjects who are anxious about participating in MRI studies are gradually desensitized to the confined space of an MRI magnet tunnel through a series of training steps. A feedback system to help train subjects to remain still when in the scanner is being developed. The mock scanner is located near the Behavioral Testing Suite, and in close proximity to the 1.5T and 3T magnets.

Histological Analysis Lab. This laboratory is equipped with a Canon digital camera, camera stand and tripod for photographing blockface images prior to sectioning. For tissue sectioning, this laboratory is equipped with a Leica 2000R microtome for cutting frozen sections. A histological staining area, immunocytochemical reagents, image analysis and stereology (MicroBrightField Bioscience, Inc.) equipment are available for quantitative analyses. Other resources include a Nikon 80i microscrope (with fluorescence and brightfield functions) (MVI, Inc, Avon MA) with motorized stage, to complement the stereology software (MicroBrightField Bioscience, Inc.). A Li-Cor Oydessy Infrared Imaging System (Licor Biosciences, Lincoln NE), located in Dr. Brad Hymanús laboratory is available to Center investigators, for digitizing histological sections.

Electronics and Machine Shops. Instrumentation for design, construction and repair activities is distributed among three locations: (1) Bay 2/Bay 3/High Field Laboratory; (2) Bay 4/Bay 5/9.4 T Lab; and (3) Photon Migration Lab. The shops are equipped with tools for working with electronic circuitry, fiber optics and mechanical devices; equipment for fabrication of printed circuit boards; instrumentation for electronic testing and measurement of digital, analog, and RF circuitry (power supplies, voltmeters, R/L/C meter, RF power meter, oscilloscopes, gaussmeters, RF sweepers, an analog impedance meter, a digital impedance analyzer, and 5 HP RF network analyzers); and machine tools (drill presses, belt sander, grinder, band saw, 13 inch lathe, small milling machine). A stock of materials, hardware and electronic components is maintained. Machine tools are available to carry out complete computer-assisted design and fabrication of probes, animal carriers, gradient coils, etc. In addition to these resources, we have access to the MGH machine shop. Design and simulation tasks are supported within the Center with Windows 2000-based multiprocessor workstations running Remcom (State College, PA) BioPro 5.2 FDTD software for simulation of electromagnetic fields, Electronics Workbench Multisim 2001 (Toronto, Canada) for simulation of electrical networks, and IMSI TurboCad (Novato, CA) for mechanical design.

RF Electronics Laboratory. The RF coil laboratory consists of a ~500 ft^2 area with 6 RF compatible work benches and 5 RF network analyzers; this space includes an electronics store-room for maintaining an extensive supply of RF parts and tools. The laboratory has a circuit board milling machine for creating circuit boards and coil layouts. There is also a 3D printer capable of making head-shaped models and helmet designs out of ABS plastic from CAD files generated from MRI volume scans (Dimension SST-1200). Additional equipment includes and RF spectrum analyzer, oscilloscopes (including a 1GHz BW digital scope), RF frequency synthesizers, and common electronics measurement and test devices.

Education and Administrative Areas. This area includes a conference room, audio-visual laboratory (equipped with computers, TV monitors, VCRs, carousels, teaching files and tapes), staff offices and general desk space for graduate students, postdoctoral fellows and junior faculty.

The Center's administration area is located on the second floor of Building 149, in area 2301. Facilities located here include fax machine, Xerox, standard and color laser printers, and faculty and staff mailboxes. This area contains faculty and secretarial office space and a conference room.

Computing Facilities

The Center's IT infrastructure consists of over 300 Linux workstations and 150 Windows and Macintosh desktops on users desks owned by individual research groups. There is a server farm of over 25 Linux servers that handles central storage, email, web and other shared services. Overall storage capacity of the center including disks in local workstations and central storage exceeds 200 terabytes. The Center also has a 128-node computing cluster for batch analysis jobs. Each node consists of two Quad Core Xeon E5472 3.0 GHz CPUs with 32GB of RAM, which together equal a total of 1024 compute cores available for batch jobs. Each node is connected by both a 1 GBit/s Ethernet link and a 20 GBit/s DDR Infiniband backplane. The Infiniband connection is used by parallelized jobs using MPI (message passing interface) to utilize multiple cores. A major project is underway now to vastly increase the amount of storage at the Center and enhance its performance capabilities to handle the load from the cluster. An install of 300TB of high performance central storage is in process now with plans to go into the petabyte range over the next few years.

The IT facilities are supported by a small IT staff comprising one full-time PhD-level manager, who directs three full-time system administrators. The Center also has three full-time programmers who support in-house-developed software tools. Available commercial software includes AVS (Advanced Visual Systems, Waltham, MA), MATLAB (The MathWorks, Natick, MA) and MEDx (Sensor Systems, Sterling, VA) for general-purpose computation, simulation and image analysis; and XWIN-NMR (Bruker BioSpin), Origin (OriginLab Corp.,

Northampton, MA), Nuts (Acorn NMR, Livermore, CA) for analysis of NMR spectra and the Siemens IDEA development environment for pulse sequences and image reconstruction software (Siemens, Erlangen, Germany). A substantial level of internal software development for image and data analysis is ongoing, using HTML, C, C++, Java, FORTRAN, Pascal, Perl and TCL/TK.

For high-performance image reconstruction the center is equipped with a custom-designed ScaleMP vSMP computer equipped with 128 Xeon E5472 3.0 GHz cores and 1TB shared RAM. It uses a 40 GBit/s QDR Infiniband backplane and is equipped with a Rackswitch G8000 48 port aggregation switch with two 10 Gbit/s Ethernet links with fiber-optic extenders for real-time data streaming from the MRI machines. It is capable of running the Siemens image reconstruction software, and can therefore be fully integrated in any of the Center's MRI machines for online image reconstruction of the very large or very high data rate scans produced by the large array coils.

Harvard Catalyst CTSC MGH General Clinical Research Center Biomedical Imaging Core

The Biomedical Imaging Core (BIC) of the MGH General Clinical Research Center, part of the Harvard Catalyst Clinical Translational Science Center (CSTC), provides translational research support, including nursing, bioengineering, pharmacy, reception, etc., for clinical/translational research studies, enabling easy coordination of the collection of additional data; for instance, behavioral testing and collection of blood for genotyping. The BIC is located in a 1,500 ft^2 space on the 2^{nd} floor of Building 149, directly above the dedicated research MR scanners and close to the MEG/EEG imaging suite. The space contains a patient reception/waiting area, 2 outpatient exam rooms, computing resources, laboratory/storage space and office space for the BIC staff.

Outpatient exam rooms are available for cognitive, pharmacological and physiological challenges and monitoring both before and during imaging. Physical examinations, cognitive testing, insertion of intravenous lines, and other patient centered activities are carried out in the exam rooms. There are four semi-private (curtains can separate the patient recliners) exam areas in one large room and two private rooms with stimulus presentation capabilities that replicate the imaging environment. The private exam rooms are sound-attenuated and equipped for performing physical exams. One of the private rooms is shielded and can be used for electrical or optical imaging studies. This electrically shielded exam room is equipped for physiological monitoring, blood sampling, and drug infusions. The modular physiological monitoring system enables non-invasive and invasive measurement of blood pressure, heart rate, EKG, oxygen saturation, temperature, skin conductance, expired oxygen and carbon dioxide concentrations and respiration rate. The outpatient exam room and Bay 4 MR suite are also equipped with medical grade air, O2 and CO2.

The BIC includes a small clinical laboratory for specimen preparation and temporary storage of specimens with centrifuges and 4^{o} and -20^{o}C refrigerator/freezer. BIC maintains code carts equipped with pediatric supplies; these code carts are stored at appropriate sites near each of the imaging systems that support invasive studies. The laboratory is outfitted with both clean and dirty areas for storage with separate wash facilities. The BIC also maintains a medication closet for storage of investigational drugs that can be dispensed on site. MGH Research Pharmacy provides logistical support for pharmacy services such as special formulations, drug procurement, storage, record keeping, study fees, inventory control, drug distribution, packaging and labeling, randomization and blinding, for compliance with federal regulations.

Office space is available within the BIC research nursing staff, biostatistician, the software developers to consult with HCP investigators as they use the BIC facilities.

Advanced Computational Image Processing and Analysis Center

The Advanced Computational Image Processing and Analysis Center (ACIPAC) is a satellite of the Martinos Center on the MIT campus, established in collaboration with the MIT Artificial Intelligence (AI) Laboratory. The closely affiliated ACIPAC has extensive resources and expertise for solving practical image processing and analysis issues relevant to biomedical imaging. This Center is an important bridge to affiliated MIT research community, and allows MIT students a direct avenue to engage in biomedical imaging research at the Martinos Center.

MGH Main Campus

The main campus of the MGH is located in [redacted], 15 minutes from the Martinos Center in [redacted]. Frequent shuttle transportation provided between the two campuses for both researchers and ambulatory patients. Resources on the main campus include MRI and PET imaging and support laboratories as well as animal housing facilities and the MGH medical library; facilities are located in several buildings across the campus.

Just In Time Report

Report submitted on : 06/12/2019 12:19 PM

IRB Confirmation:	No IRB Certification was required
Human Subjects Assurance Number:	No Human Subjects Assurance was required
IACUC Confirmation:	No IACUC Certification was required

OTHER SUPPORT

Paul Wighton, PhD

Commons ID: [redacted]

ACTIVE

R42 CA183150-03 (PD/**PI**: **Wighton**, van der Kouwe) NIH-NCI 04/01/2018 - 3/31/2020 3.6 cal.
AutoRegister: A System For Enhancing Accuracy of Tumor Change Detection
A project to develop a software system allowing accurate real-time registration of MR images of the brain such that the error introduced by varying head placement does not effect the measurement of the size of a tumor.

R44 NS089090-03 (PD/PI: Schmansky, Fischl) NIH-NINDS 09/01/2017 - 08/31/2019 1.2 cal.
MRI brain morphometry for computer-aided detection of neurological disorders
In this project we seek to (1) integrate novel deep-learning and Random Forest-based patch-matching image synthesis technology into FreeSurfer to make it robust to variations in scanner platform and acquisition parameters, (2) use modern parallel-processing to reduce execution time to a clinically-feasible length, and (3) develop the code in an FDA compliant manner.

R01 HD093578-01 (PI: van der Kouwe) NIH-NICHD 09/08/2018 - 05/31/2022 2.4 cal.
Neuroimaging and gut microbiome markers of development in HIV-exposed uninfected infants
This project investigates the relationship between maternal HIV infection, breast milk composition, the developing infant gut microbiome, and the developing infant brain.

PENDING

OVERLAP

There is no scientific overlap. To accommodate the effort required for grant R42 AG062026-01A1, effort was reduced in grants R44 NS089090-03 and R42 CA183150-03.

OTHER SUPPORT

Bruce Fischl, PhD

Commons ID: [redacted]

ACTIVE

5P41EB015896-20 (Rosen) 08/01/14-05/31/20 1.2 cal
NIH/NCRR Project Leader.Fischl [redacted]
Center for Functional Imaging Technologies
In this application we seek renewed support for our continued efforts to develop innovative neuroimaging technologies within the highly integrated multimodal framework of our P41 Regional Resource. The overarching goal of the CFNT is to provide technology resources to more closely examine and better understand the human brain in both health and disease.

5R01NS083534-05 Fischl 05/01/14-03/31/20 0.12 cal
NIH [redacted]
A Longitudinal Analysis stream for FreeSurfer
The successful completion of the proposed project would provide a set of accurate, specific and sensitive tools to the thousand of clinicians and researchers that currently use FreeSurfer.

2P01AG036694-06 (Sperling, Core PI: Johnson) 07/01/15-06/30/20 0.30 cal
NIH [redacted]
Impact of Amyloid and Tau on the Aging Brain: The Harvard Aging Brain Study - Core C
The Harvard Aging Brain Study Program Project Grant seeks to understand the earliest brain changes that will predict whether an older individual will develop memory loss and eventual cognitive decline associated with Alzheimer's disease or whether they will demonstrate resilient brain aging.

5R01EB019956-04 (Fischl) 08/20/15-06/30/20 1.92 cal
NIH [redacted]
Algorithms for MR and OCT-based Architectonic and Laminar Segmentation
Automated segmentation of cortical areas and laminar boundaries will enable new and more specific types of analysis of neuroimaging data. In particular, the ability to probe laminar properties of specific cortical areas may provide significant advances in developmental disorders such as autism, schizophrenia and dyslexia.

5R21DK108277-02 (Fischl) 09/20/15-08/31/19 0.12 cal
NIH [redacted]
Auto Calibration and shaped insulin delivery to lower average blood glucose
The successful completion of this project would result in algorithms that would be easy to integrate into existing pump technology and could reduce average BG levels in millions of T1D patients by 50-70 mg/dL or more, corresponding to a two percentage point drop in A1C.

5U24DA041123-04 S/C University of California San Diego (Dale) 09/30/15-05/31/20 0.12 cal
NIH (PI of S/C- Polimeni) [redacted]
2/13 ABCD-USA Consortium: Data Analysis Center
The MGH site will take on two essential tasks as part of the overall Data Acquisition and Analysis Core activities. First, the MGH will have primary responsibility for the design, testing and evaluation, distribution and support for the data collection sites nationwide that use the Siemens platform. Second, MGH team members Drs. Fischl and Greve will work with the data analysis group at UCSD to assure that the highly utilized Freesurfer morphometric and functional analysis stream is fully integrated into the overall data analysis

1U01AG052564-03 (Van Essen PI WASHU) 08/19/16-05/31/20 0.12 cal
NIHAG Salat PI MGH SC [redacted]
Mapping the Human Connectome During Typical Aging
This project will use structural and functional imaging methods to characterize brain circuitry in a large population of health older adults, from ages 36 to 100+. It will enable assessment of changes in brain circuits and brain behavior relationships during typical aging.

1R01EB023281-03 (Greve) 09/15/16-06/30/20 0.84 cal
NIH [redacted]
Free Surfer Development, Maintenance, and Hardening
This proposal will allow for continued support of FreeSurfer from the developers as well as new development to make FreeSurfer faster, more robust, and easier to interpret.

1R44NS089090-01A1 S/C CorticoMetrics 09/01/15-8/31/19 0.12 cal
NIH (Schmansky PD/PI prime PI of S/C Fischl) [redacted]
MRI Brain Morphometry for Computer-Aided Detection of Neurological Disorders
As part of the proposed project "MRI brain morphometry for computer-aided detection of neurological disorders", we will research and develop software which will make the processing of T1 structural images by the FreeSurfer software package robust to variations in scanner parameters.

U24NS100591 (PI: Greenberg) 09/01/16 - 08/31/21 0.12 CM
NIH/NINDS/NIA [redacted]
VCID Biomarker's Coordination Center
The purpose of this project is to establish the Coordinating Center for the new Small Vessel Vascular Contributions to Cognitive Impairment and Dementia (VCID) Biomarkers Consortium.

5U01NS086625-04 (Gordon-Mt Sinai School of Medicine) 01/01/14-12/31/19 0.12 cal
NIH S/C (Fischl PI-S/C) [redacted]
Neuropathology of CTE and Delayed Effects of TBI: Toward In-Vivo Diagnostics
In this project, our multi-disciplinary team of neuroimagers, physicists, engineers, neurologists, and pathologists will develop and validate novel MRI sequences for ex vivo imaging of human brain specimens.

2P30DK040561 (Grinspoon) 08/01/17-07/31/22 0.36 cal
NIH/NIDDK [redacted]
Nutrition Obesity Research Center at Harvard (NORCH)
This Center grant supports the Nutrition Obesity Research Center at Harvard (NORC-H), the goals of which are to provide critical support to research in nutrition and obesity throughout the Harvard community, to facilitate novel directions in nutrition and obesity research through pilot funding and scientific exchange, to promote interactions and collaborations among investigators to advance the science of nutrition and obesity, and to foster the development of junior faculty in these research areas.
Role: Sub-Core Director, Metabolic Imaging Core

1U01MH117023-01 (Fischl) 08/22/18-05/31/23 3.0 cal
NIH-NIMH [redacted]
Imaging and Analysis Techniques to Construct a Cell Census Atlas of the Human Brain
In this project, we will image across this vast range of scales to create a multiscale atlas akin to Google Earth for the human brain that can visualize hemisphere-wide networks and then zoom in to see individual, labeled cells at micron resolution in the frontal temporal lobe.

1R01NS105820-01A1(Fischl) 12/01/18-11/30/23 1.42 cal
NIH-NINDS [redacted]
Segmenting Brain Structures for Neurologic Disorders
Successful completion of the proposed project will greatly increase the number of structures and level of detail of publicly available segmentation tools. These new capabilities will enable other studies to significantly

increase their ability to detect disease effects in research settings as well as phase II and phase III clinical trials.

R01AG059011-01A1 (Jacques/Miller) 04/01/19-03/31/24 0.60 cal
NIH/NIA/Tufts University
[redacted]
Vitamin B12 status, cognitive decline and incident dementia
The major goals of this project are, we will analyze the scans that are of sufficient quality from 600 subjects who had FHS MRI scans from 2005-2011 and a follow-up scan from 2011-2016 that are of sufficient quality to yield interpretable results. For each of these scans we will apply our standard volumetric analysis as well as segment hippocampal subfields and apply longitudinal analysis tools. Finally, we will perform extensive quality control on the resulting morphometric measures using custom-built in-house tools capable of facilitating visual inspection of these large sized datasets
Role: Co-Investigator

PENDING

[redacted]

OVERLAP

If the pending grant is awarded, Dr. Fischl will work with MGH Administrators to adjust his efforts as follows so as not to exceed 12 calendar months:

5R01NS083534-05 Fischl - Dr. Fischl reduced his effort from .96 to .12 cal months

There is no scientific overlap.

OTHER SUPPORT

Nicholas J. Schmansky

Commons ID: [redacted]

ACTIVE

R42 CA183150-03 (PD/PI: Wighton, van der Kouwe) NIH-NCI 04/01/2018 - 3/31/2020 1.2 cal.
AutoRegister: A System For Enhancing Accuracy of Tumor Change Detection
A project to develop a software system allowing accurate real-time registration of MR images of the brain such that the error introduced by varying head placement does not effect the measurement of the size of a tumor.

R44 NS089090-03 (**PD**/PI: **Schmansky**, Fischl) NIH-NINDS 09/01/2017 - 08/31/2019 8.4 cal.
MRI brain morphometry for computer-aided detection of neurological disorders
In this project we seek to (1) integrate novel deep-learning and Random Forest-based patch-matching image synthesis technology into FreeSurfer to make it robust to variations in scanner platform and acquisition parameters, (2) use modern parallel-processing to reduce execution time to a clinically-feasible length, and (3) develop the code in an FDA compliant manner.

PENDING

[redacted]

OVERLAP

There is no scientific overlap. To accommodate the effort required for grant R42 AG062026-01A1, effort was reduced in grant R44 NS089090-03.

OTHER SUPPORT

Lee Tirrell

Commons ID: [redacted]

ACTIVE

R42 CA183150-03 (PD/PI: Wighton, van der Kouwe) NIH-NCI 04/01/2018 - 3/31/2020 1.2 cal.
AutoRegister: A System For Enhancing Accuracy of Tumor Change Detection
A project to develop a software system allowing accurate real-time registration of MR images of the brain such that the error introduced by varying head placement does not effect the measurement of the size of a tumor.

R44 NS089090-03 (PD/PI: Schmansky, Fischl) NIH-NINDS 09/01/2017 - 08/31/2019 9.6 cal.
MRI brain morphometry for computer-aided detection of neurological disorders
In this project we seek to (1) integrate novel deep-learning and Random Forest-based patch-matching image synthesis technology into FreeSurfer to make it robust to variations in scanner platform and acquisition parameters, (2) use modern parallel-processing to reduce execution time to a clinically-feasible length, and (3) develop the code in an FDA compliant manner.

PENDING

[redacted]

OVERLAP

There is no scientific overlap. To accommodate the effort required for grant R42 AG062026-01A1, effort was reduced in grant R44 NS089090-03.

The Commonwealth of Massachusetts

Secretary of the Commonwealth

[redacted]

William Francis Galvin
Secretary of the
Commonwealth

Date: [redacted]

To Whom It May Concern :

I hereby certify that a certificate of organization of Limited Liability Company was filed in this office by

[redacted]

in accordance with the provisions of Massachusetts General Laws, Chapter 156C, on

[redacted]

I further certify that said Limited Liability Company has not filed a Certificate of Cancellation; that said Limited Liability Company has not been administratively dissolved; and that, so far as appears of record, said Limited Liability Company has legal existence.

In testimony of which,
I have hereunto affixed the
Great Seal of the Commonwealth
on the date first above written.

[redacted]

Secretary of the Commonwealth

[redacted]

The Commonwealth of Massachusetts
William Francis Galvin

Secretary of the Commonwealth, Corporations Division

[redacted]

Minimum Fee: [redacted]

Annual Report
(General Laws, Chapter)

Identification Number: [redacted]

Annual Report Filing Year: 2019

1.a. Exact name of the limited liability company: CORTICOMETRICS, LLC

1.b. The exact name of the limited liability company *as amended*, is: CORTICOMETRICS, LLC

2a. Location of its principal office:

No. and Street: [redacted]
City or Town: [redacted] State: [redacted] Zip: [redacted] Country: [redacted]

2b. Street address of the office in the Commonwealth at which the records will be maintained:

No. and Street: [redacted]
City or Town: [redacted] State: [redacted] Zip: [redacted] Country: [redacted]

3. The general character of business, and if the limited liability company is organized to render professional service, the service to be rendered:

DEVELOPMENT & SALE OF SOFTWARE FOR CLINICAL DIAGNOSIS & DECISION SUPPORT O F NEUROLOGICAL DISORDERS

4. The latest date of dissolution, if specified:

5. Name and address of the Resident Agent:

Name: [redacted]
No. and Street: [redacted]
City or Town: [redacted] State: [redacted] Zip: [redacted] Country: [redacted]

6. The name and business address of each manager, if any:

Title	Individual Name First, Middle, Last, Suffix	Address (no PO Box) Address, City or Town, State, Zip Code
MANAGER	NICHOLAS JOHN SCHMANSKY	[redacted]

7. The name and business address of the person(s) in addition to the manager(s), authorized to execute documents to be filed with the Corporations Division, and at least one person shall be named if there are no managers.

8. The name and business address of the person(s) authorized to execute, acknowledge, deliver and record any recordable instrument purporting to affect an interest in real property:

Title	**Individual Name** First, Middle, Last, Suffix	**Address** (no PO Box) Address, City or Town, State, Zip Code

9. Additional matters:

SIGNED UNDER THE PENALTIES OF PERJURY, this 29 Day of May, 2019,
NICHOLAS J. SCHMANSKY **, Signature of Authorized Signatory.**

THE COMMONWEALTH OF MASSACHUSETTS

I hereby certify that, upon examination of this document, duly submitted to me, it appears that the provisions of the General Laws relative to corporations have been complied with, and I hereby approve said articles; and the filing fee having been paid, said articles are deemed to have been filed with me on:

May 29, 2019 02:39 PM

WILLIAM FRANCIS GALVIN

Secretary of the Commonwealth

CorticoMetrics, LLC
Profit & Loss
All Transactions

	May 30, 19
Ordinary Income/Expense	
Income	
4000 · Revenue	
4030 · Grant Revenue	
4000 · Revenue - Other	
Total 000 · Revenue	
Total Income	
Cost of Goods Sold	
5000 · Direct Costs	
5100 · Direct Labor	
5200 · Direct Materials	
5300 · Direct Subcontractors	
5400 · Direct Consultants	
5500 · Direct Equipment	
5600 · Direct Travel	
5700 · Other Direct Costs	
Total 5000 · Direct Costs	
Total COGS	
Gross Profit	
Expense	
5900 · IRD Expenses	
5910 · IRD Labor	
Total 5900 ·IRD Expenses	
6000 · Fringe Benefits	
6100 · Sick Pay	
6110 · Vacation Pay	
6120 · Holiday Pay	
6200 · Employee Health Insurance	
6210 · Employee Dental Insurance	
6400 · Pension Plan Contribution	
6500 · Payroll Taxes	
6600 · Payroll Service Fees	
Total 6000 · Fringe Benefits	
7000 · Indirect Expenses	
7100 · Indirect Labor	
7150 · Casual Labor	
7200 · Bank Fees	
7210 · Postage and Delivery	
7230 · Office Supplies and Expense	
7240 · Computer Supplies	
7250 · Dues and Subscriptions	
7260 · Advertising and Promotion	
7320 · Indirect Travel	
7330 · Licenses and Permits	
7400 · Rent	
7410 · Utilities	
7420 · Telephone	
7430 · Business Insurance	
7600 · Meetings and Seminars	
7610 · Printing and Reproduction	
7900 · Miscellaneous	
8100 · G & A Labor	
8110 · G & A Travel Expenses	
8120 · Other G & A Expense	
8300 · Professional Fees-Legal General	
8310 · Professional Fees-Accounting Tax	

CorticoMetrics, LLC
Profit & Loss
All Transactions

	May 30, 19
8900 · State Income Tax	[redacted]
8910 · Annual Report	[redacted]
Total 7000 · Indirect Expenses	[redacted]
9000 · Unallowable Costs	[redacted]
6150 · Bonus	
9100 · Alcohol, Meals Ent-Unallowable	
9300 · Interest Expense	
9420 · Legal Fees-Unallowable	
9430 · Automobile Expense	
9600 · Adv., Sales and Marketing	
9000 · Unallowable Costs - Other	
Total 9000 · Unallowable Costs	[redacted]
Total Expense	[redacted]
Net Ordinary Income	[redacted]
Net Income	[redacted]

CorticoMetrics, LLC
Balance Sheet
All Transactions

	May 30, 19
ASSETS	
Current Assets	
Checking/Savings	
1000 · Checking - Bank of America	[redacted]
Total Checking/Savings	[redacted]
Other Current Assets	
1110 · Unbilled Receivables	[redacted]
1410 · Prepaid Insurance	[redacted]
Total Other Current Assets	[redacted]
Total Current Assets	[redacted]
Other Assets	
1900 · Security Deposits	[redacted]
Total Other Assets	[redacted]
TOTAL ASSETS	[redacted]
LIABILITIES & EQUITY	
Liabilities	
Current Liabilities	
Credit Cards	
Credit Card at Bank of America	[redacted]
Total Credit Cards	[redacted]
Total Current Liabilities	[redacted]
Total Liabilities	[redacted]
Equity	
3300 · Distributions	[redacted]
Net Income	[redacted]
Total Equity	[redacted]
TOTAL LIABILITIES & EQUITY	[redacted]

SAM SYSTEM FOR AWARD MANAGEMENT

Nicholas Schmansky Log Out

MY SAM | SEARCH RECORDS | DATA ACCESS | CHECK STATUS | ABOUT | HELP | Search

ALERT: June 11, 2018: Entities registering in SAM must submit a notarized letter appointing their authorized Entity Administrator. Read our updated FAQs to learn more about changes to the notarized letter review process and other system improvements.

ALERT: SAM.gov will be down for scheduled maintenance from Friday, June 14, 2019 at 9:00 AM until Monday, June 17, 2019 6:00 AM (EDT).

ALERT: CAGE is currently experiencing a high volume of registrations, and is working them in the order in which they are received. When your registration is assigned to a CAGE Technician, you will be contacted by CAGE, if necessary, for any additional information.

Entity Dashboard

- Entity Overview
- Entity Registration
  - Core Data
  - Assertions
  - Reps & Certs
  - POCs
- Reports
  - Service Contract Report
  - BioPreferred Report
- Exclusions
  - Active Exclusions
  - Inactive Exclusions
  - Excluded Family Members

BACK TO USER DASHBOARD

CORTICOMETRICS LLC
DUNS: [redacted] **CAGE Code: 5EJM2**
Status: Active
Expiration Date: 03/24/2020
Purpose of Registration: Federal Assistance Awards Only

[redacted]

Entity Overview

Entity Registration Summary

DUNS: [redacted]
Name: CORTICOMETRICS LLC
Business Type: Business or Organization
Last Updated By: Nicholas Schmansky
Registration Status: Active
Activation Date: 04/09/2019
Expiration Date: 03/24/2020

Exclusion Summary

Active Exclusion Records? No

EVALUATION OF FINANCIAL MANAGEMENT SYSTEMS (Abbreviated Questionnaire)*			
	YES	NO	COMMENT
A. ACCOUNTING SYSTEM:			
1. Is there a chart of accounts?	**YES**		
2. Does the accounting system include a project cost ledger providing for the recording of expenditures for each program by required budget cost categories?	**YES**		The accounting firm of Jameson & Co. CPAs (https://www.jamesoncpa.com/) manages CorticoMetrics' accounting system. They are specialists in government grant accounting (including NIH STTR/SBIR grants). Their accounting system tracks costs between direct and indirect costs (general ledger) as well as direct costs by project (project ledger). They use QuickBooks, with an appropriate Chart of Accounts.
3. How do employees account for their time and effort? Please explain.			Each employee must fill-out a timesheet that shows the number of hours worked in each project (direct labor) or indirect labor category.
B. FINANCIAL CAPABILITY:			
1. Does the organization prepare financial statements at least annually? (Provide a copy of latest Balance Sheet and Income Statement.)	**YES**		Balance Sheet and Profit/Loss Statement attached.
2. Has the organization established line(s) of credit? If so, identify source and amount.	**YES**		Credit card with Bank of America, credit limit [redacted]
C. BUDGETARY CONTROLS:			
1. Are there budgetary controls in effect (e.g. comparison of budget with actual expenditures on a monthly basis) to preclude drawing down federal funds in excess of:			Jameson & Co. runs a monthly 'backlog' function on the budget to report on expenditures, relative to the Notice of Awards.
a. Total funds authorized on the Notice of Grant Award;	**YES**		
b. Total funds available for any cost category if restricted on the Notice of Grant Award.	**YES**		
D. INTERNAL CONTROLS			
1. What safeguards has the grantee instituted to ensure adequate internal controls in the company? Please describe. Some examples might be:			
a. Accounting entries are supported by appropriate documentation; e.g. purchase orders and vouchers.	**YES**		

	YES	NO	COMMENT
b. Separation of responsibility in the receipt, payment, and recording of cash.	**YES**		Company CEO submits and approves invoices and timesheets. Jameson & Co. manages payments and PMS draw-downs.
c. Other			

STTR Funding Agreement Certification

Grant Application Number: 1 R42 AG062026-01A1

Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)): Paul Wighton, PhD, Bruce Fischl PhD

All small businesses that are selected for award of an STTR funding agreement must complete this certification at the time of award and any other time set forth in the Notice of Award that is prior to performance of work under this award. This includes checking all of the boxes and having an authorized officer of the awardee sign and date the certification each time it is requested.

Please read carefully the following certification statements. The Federal government relies on this information to determine whether the business is eligible for a Small Business Technology Transfer (STTR) Program award. A similar certification will be used to ensure continued compliance with specific program requirements during the life of the funding agreement. The definitions for the terms used in this certification are set forth in the Small Business Act, SBA regulations (13 C.F.R. Part 121), the SBIR Policy Directive and also any statutory and regulatory provisions references in those authorities.

If the Grants Management Officer believes that the business may not meet certain eligibility requirements at the time of award, they are required to file a size protest with the U.S. Small Business Administration (SBA), who will determine eligibility. At that time, SBA will request further clarification and supporting documentation in order to assist in the verification of any of the information provided as part of a protest. If the Grants Management Officer believes, after award, that the business is not meeting certain funding agreement requirements, the agency may request further clarification and supporting documentation in order to assist in the verification of any of the information provided.

Even if correct information has been included in other materials submitted to the Federal government, any action taken with respect to this certification does not affect the Government's right to pursue criminal, civil, or administrative remedies for incorrect or incomplete information given in the certification. Each person signing this certification may be prosecuted if they have provided false information.

The undersigned has reviewed, verified and certifies that (all boxes must be checked):

1. The business concern meets the ownership and control requirements set forth in 13 C.F.R. § 121.702.

   ☒ Yes ☐ No

2. If a corporation, all corporate documents (articles of incorporation and any amendments, articles of conversion, by-laws and amendments, shareholder meeting minutes showing director elections, shareholder meeting minutes showing officer elections, organizational meeting minutes, all issued stock certificates, stock ledger, buy-sell agreements, stock transfer agreements, voting agreements, and documents relating to stock options, including the right to convert non-voting stock or debentures into voting stock) evidence that it meets the ownership and control requirements set forth in 13 C.F.R. § 121.702.

   ☐ Yes ☐ No ☒ N/A Explain why N/A: LLC (see 4.)

3. If a partnership, the partnership agreement evidences that it meets the ownership and control requirements set forth in 13 C.F.R. § 121.702.

   ☐ Yes ☐ No ☒ N/A Explain why N/A: LLC (see 4.)

4. If a limited liability company, the articles of organization and any amendments, and operating agreements and amendments, evidence that it meets the ownership and control requirements set forth in 13 C.F.R. § 121.702.

   ☒ Yes ☐ No ☐ N/A Explain why N/A:

5. The birth certificates, naturalization papers, or passports show that any individuals it relies upon to meet the eligibility requirements are U.S. citizens or permanent resident aliens in the United States.

   ☒ Yes ☐ No ☐ N/A Explain why N/A:

6. It has no more than 500 employees, including the employees of its affiliates.

   ☒ Yes ☐ No

7. SBA has not issued a size determination currently in effect finding that this business concern exceeds the 500 employee size standard.

   ☒ Yes ☐ No

8. During the performance of the award, the principal investigator will spend more than half of his/her time as an employee of the awardee or the research institution, or the principal investigator has requested and received a written deviation from this requirement from the Grants Management Officer.

   ☒ Yes ☐ No Deviation approved in writing by Grants Management Officer: %

9. All, essentially equivalent work, or a portion of the work proposed under this project (check the applicable line):

   ☒ Has not been submitted for funding by another Federal agency

   ☐ Has been submitted for funding by another Federal agency but has not been funded under any other Federal grant, contract, subcontract, or other transaction.

   ☐ A portion has been funded by another grant, contract, or subcontract as described in detail in the proposal and approved in writing by the Grants Management Officer.

10. During the performance of award, it will perform the applicable percentage of work unless a deviation from this requirement is approved in writing by the Grants Management Officer (check the applicable line and fill in if needed):

    ☒ STTR Phase I: at least forty percent (40%) of the research

    ☐ STTR Phase II: at least forty percent (40%) of the research

    ☐ Deviation approved in writing by the Grants Management Officer: %

11. During performance of award, the research/research and development will be performed in the United States unless a deviation is approved in writing by the Grants Management Officer.

    ☒ Yes ☐ No

12. During the performance of award, the research/research and development will be performed at my facilities with my employees, except as otherwise indicated in the STTR application and approved in the Notice of Award.

    ☒ Yes ☐ No

13. It has registered itself on SBA's database as majority-owned by venture capital operating companies, hedge funds or private equity firms.

    ☐ Yes ☒ No ☐ N/A Explain why N/A:

14. The small business concern has provided satisfactory evidence that it will exercise management direction and control of the performance of the STTR funding agreement.

    ☒ Yes ☐ No

    It will notify the Federal agency immediately if all or a portion of the work proposed is subsequently funded by another Federal agency.

    ☒ Yes ☐ No

I understand that the information submitted may be given to Federal, State and local agencies for determining violations of law and other purposes.

I am an officer of the business concern authorized to represent it and sign this certification on its behalf. By signing this certification, I am representing on my own behalf, and on behalf of the business concern that the information provided in this certification, the application, and all other information submitted in connection with this application, is true and

correct as of the date of submission. I acknowledge that any intentional or negligent misrepresentation of the information contained in this certification may result in criminal, civil or administrative sanctions, including but not limited to: (1) fines, restitution and/or imprisonment under 18 U.S.C. § 1001; (2) treble damages and civil penalties under the False Claims Act (31 U.S.C. § 3729 et seq); (3) double damages and civil penalties under the Program Fraud Civil Remedies Act (31 U.S.C. §3801 et seq); (4) civil recovery of award funds; (5) suspension and/or debarment from all Federal procurement and nonprocurement transactions (FAR Subpart 9.4 or 2 C.F.R. part 180; and (6) other administrative penalties including termination of SBIR/STTR awards.

June 7, 2019 Date	[redacted]
NJS Signature	
Nicholas John Schmansky Printed Name (First, Middle, Last)	
Co-Founder, CEO Title	
CorticoMetrics LLC Organization Name	

NIH SMALL BUSINESS TECHNOLOGY TRANSFER PROGRAM
SMALL BUSINESS CONCERN VERIFICATION STATEMENT

Grant Application Number: 1 R42 AG062026-01A1
Organization: CorticoMetrics LLC
Project Director(s)/Principal Investigator(s) (PD(s)/PI(s): Paul Wighton, PhD, Bruce Fischl, PhD

The Small Business Technology Transfer (STTR) program legislation requires that the applicant small business concern (SBC) be eligible at the time of the award. As the responsible Federal staff for administering NIH grant funds, Grants Management Officials of the NIH Institutes and Centers (ICs) must verify eligibility prior to issuing a Notice of Grant Award. If the SBC is affiliated with any other organization (domestic or foreign), see www.sba.gov/size.

If an application is selected for funding under the STTR program, no award will be issued until the NIH IC receives and accepts the following information, which may be provided in a format of your choosing or by completing a checklist as in the example below:

☒ 1 The above-named organization is a for-profit United States SBC that is at least 51% owned and controlled by one or more *individuals* who are citizens of, or permanent resident aliens in, the United States, or in the case of a publicly-owned business, at least 51% of its voting stock is owned by United States citizens or lawfully admitted permanent resident aliens.

Complete the following part of (1) if relevant: If the above-named applicant organization has been determined by the Small Business Administration (SBA) to be "other than small" for a size standard of not more than 500 employees or for purposes of the SBIR program:

Have you been recertified by SBA? ☐ Yes ☐ No
If not recertified, have you requested a recertification by SBA for eligibility under the SBIR program? ☐ Yes ☐ No

☒ 2 The above-named organization is independently owned and operated, is not dominant in the field of operation in which it is proposing, has its principal place of business located in the United States, has, including its affiliates, 500 or fewer employees, is not involved in a merger/acquisition that is near complete, and meets the other regulatory requirements found in Title 13, Code of Federal Regulations (CFR), Part 121. (Note that the SBA considers "agreements to merge (including agreements in principle) to have present effect on the power to control a concern" [Section 121.103(d)(1) of 13 CFR 121]).

☒ 3 The *research space* occupied by the above-named organization is available to and under the control of the above-named organization *for the conduct of its portion of the proposed project.*

☒ 4 All research on the above-referenced grant will be *performed in its entirety* in the United States, unless otherwise approved by the Grants Management Officer prior to issuance of an award.

☒ 5 The above named PD(s)/PI(s) has (have) a formal appointment with or commitment to the above-named organization, which is characterized by an official relationship between the organization and the PD(s)/PI(s), whose effort on this project will be not less than 10% of his or her total professional effort. For Multiple PD/PI projects, each PD/PI must commit a minimum of 1.2 calendar months (10% effort) to the project.

☒ 6 It is understood that the Public Health Service will not support any *market research* under its STTR program (see "Definitions," SBIR/STTR SF424 (R&R) Application Guide) or literature searches that will lead to a new or expanded statement of work, and that if an award is made, any such costs, if requested in the application, will be removed prior to award.

☒ 7 In conducting the joint research and development proposed in this project, the above-named applicant SBC will conduct not less than 40% of the work and the single, "partnering" research institution named in the application will perform not less than 30% of the work.

☒ 8 It is understood that if this project is funded, drawing NIH award funds from the HHS Payment Management System serves as certification that the above-named organization has in place written policies and procedures for financial and business management systems that comply with 45 CFR 74 and the NIH Grants Policy Statement (12/03) and will follow those policies and procedures.

My signature is verification that the statements checked (□) above are true and complete. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

Nicholas J Schmansky
Co-Founder & CEO, CorticoMetrics LLC
(Official Authorized to Sign for the Organization)

June 7, 2019
(Date)

[redacted]

DN: cn=Nick Schmansky, o=CorticoMetrics LLC, ou, email=nicks@corticometrics.com, c=US
Date: 2019.06.07 12:21:24 -04'00'

Just In Time Report

Report submitted on : 06/11/2019 04:42 PM

IRB Confirmation:	No IRB Certification was required
Human Subjects Assurance Number:	No Human Subjects Assurance was required
IACUC Confirmation:	No IACUC Certification was required

OTHER SUPPORT

Paul Wighton, PhD

Commons ID: [redacted]

ACTIVE

R42 CA183150-03 (PD/**PI**: **Wighton**, van der Kouwe) NIH-NCI 04/01/2018 - 3/31/2020 7.2 cal.
AutoRegister: A System For Enhancing Accuracy of Tumor Change Detection
A project to develop a software system allowing accurate real-time registration of MR images of the brain such that the error introduced by varying head placement does not effect the measurement of the size of a tumor.

R44 NS089090-03 (PD/PI: Schmansky, Fischl) NIH-NINDS 09/01/2017 - 08/31/2019 2.4 cal.
MRI brain morphometry for computer-aided detection of neurological disorders
In this project we seek to (1) integrate novel deep-learning and Random Forest-based patch-matching image synthesis technology into FreeSurfer to make it robust to variations in scanner platform and acquisition parameters, (2) use modern parallel-processing to reduce execution time to a clinically-feasible length, and (3) develop the code in an FDA compliant manner.

R01 HD093578-01 (PI: van der Kouwe) NIH-NICHD 09/08/2018 - 05/31/2022 2.4 cal.
Neuroimaging and gut microbiome markers of development in HIV-exposed uninfected infants
This project investigates the relationship between maternal HIV infection, breast milk composition, the developing infant gut microbiome, and the developing infant brain.

PENDING

OVERLAP

There is no scientific overlap. To accommodate the effort required for grant R42 AG062026-01A1, effort will be reduced in grants R44 NS089090-03 and R42 CA183150-03.

OTHER SUPPORT

Bruce Fischl, PhD

Commons ID: [redacted]

ACTIVE

5P41EB015896-20 (Rosen) 08/01/14-05/31/20 1.2 cal
NIH/NCRR Project Leader.Fischl [redacted]
Center for Functional Imaging Technologies
In this application we seek renewed support for our continued efforts to develop innovative neuroimaging technologies within the highly integrated multimodal framework of our P41 Regional Resource. The overarching goal of the CFNT is to provide technology resources to more closely examine and better understand the human brain in both health and disease.

5R01NS083534-05 Fischl 05/01/14-03/31/20 .96 cal
NIH [redacted]
A Longitudinal Analysis stream for FreeSurfer
The successful completion of the proposed project would provide a set of accurate, specific and sensitive tools to the thousand of clinicians and researchers that currently use Free surfer.

2P01AG036694-06 (Sperling, Core PI: Johnson) 07/01/15-06/30/20 0.30 cal
NIH [redacted]
Impact of Amyloid and Tau on the Aging Brain: The Harvard Aging Brain Study - Core C
The Harvard Aging Brain Study Program Project Grant seeks to understand the earliest brain changes that will predict whether an older individual will develop memory loss and eventual cognitive decline associated with Alzheimer's disease or whether they will demonstrate resilient brain aging.

5R01EB019956-04 (Fischl) 08/20/15-06/30/20 1.92 cal
NIH [redacted]
Algorithms for MR and OCT-based Architectonic and Laminar Segmentation
Automated segmentation of cortical areas and laminar boundaries will enable new and more specific types of analysis of neuroimaging data. In particular, the ability to probe laminar properties of specific cortical areas may provide significant advances in developmental disorders such as autism, schizophrenia and dyslexia.

5R21DK108277-02 (Fischl) 09/20/15-08/31/19 0.12 cal
NIH [redacted]
Auto Calibration and shaped insulin delivery to lower average blood glucose
The successful completion of this project would result in algorithms that would be easy to integrate into existing pump technology and could reduce average BG levels in millions of T1D patients by 50-70 mg/dL or more, corresponding to a two percentage point drop in A1C.

5U24DA041123-04 S/C University of California San Diego (Dale) 09/30/15-05/31/20 .12 cal
NIH (PI of S/C- Polimeni) [redacted]
2/13 ABCD-USA Consortium: Data Analysis Center
The MGH site will take on two essential tasks as part of the overall Data Acquisition and Analysis Core activities. First, the MGH will have primary responsibility for the design, testing and evaluation, distribution and support for the data collection sites nationwide that use the Siemens platform. Second, MGH team members Drs. Fischl and Greve will work with the data analysis group at UCSD to assure that the highly utilized Freesurfer morphometric and functional analysis stream is fully integrated into the overall data analysis

1U01AG052564-03 (Van Essen PI WASHU) 08/19/16-05/31/20 0.12 cal
NIHAG Salat PI MGH SC [redacted]
Mapping the Human Connectome During Typical Aging
This project will use structural and functional imaging methods to characterize brain circuitry in a large population of health older adults, from ages 36 to 100+. It will enable assessment of changes in brain circuits and brain behavior relationships during typical aging.

1R01EB023281-03 (Greve) 09/15/16-06/30/20 .84 cal
NIH [redacted]
Free Surfer Development, Maintenance, and Hardening
This proposal will allow for continued support of FreeSurfer from the developers as well as new development to make FreeSurfer faster, more robust, and easier to interpret.

1R44NS089090-01A1 S/C CorticoMetrics 09/01/15-8/31/19 0.12 cal
NIH (Schmansky PD/PI prime PI of S/C Fischl) [redacted]
MRI Brain Morphometry for Computer-Aided Detection of Neurological Disorders
As part of the proposed project "MRI brain morphometry for computer-aided detection of neurological disorders", we will research and develop software which will make the processing of T1 structural images by the FreeSurfer software package robust to variations in scanner parameters.

U24NS100591 (PI: Greenberg) 09/01/16 - 08/31/21 0.12 CM
NIH/NINDS/NIA [redacted]
VCID Biomarker's Coordination Center
The purpose of this project is to establish the Coordinating Center for the new Small Vessel Vascular Contributions to Cognitive Impairment and Dementia (VCID) Biomarkers Consortium.

5U01NS086625-04 (Gordon-Mt Sinai School of Medicine) 01/01/14-12/31/19 0.12 cal
NIH S/C (Fischl PI-S/C) [redacted]
Neuropathology of CTE and Delayed Effects of TBI: Toward In-Vivo Diagnostics
In this project, our multi-disciplinary team of neuroimagers, physicists, engineers, neurologists, and pathologists will develop and validate novel MRI sequences for ex vivo imaging of human brain specimens.

2P30DK040561 (Grinspoon) 08/01/17-07/31/22 0.36 cal
NIH/NIDDK $7,552
Nutrition Obesity Research Center at Harvard (NORCH)
This Center grant supports the Nutrition Obesity Research Center at Harvard (NORC-H), the goals of which are to provide critical support to research in nutrition and obesity throughout the Harvard community, to facilitate novel directions in nutrition and obesity research through pilot funding and scientific exchange, to promote interactions and collaborations among investigators to advance the science of nutrition and obesity, and to foster the development of junior faculty in these research areas.
Role: Sub-Core Director, Metabolic Imaging Core

1U01MH117023-01 (Fischl) 08/22/18-05/31/23 3.0 cal
NIH-NIMH [redacted]
Imaging and Analysis Techniques to Construct a Cell Census Atlas of the Human Brain
In this project, we will image across this vast range of scales to create a multiscale atlas akin to Google Earth for the human brain that can visualize hemisphere-wide networks and then zoom in to see individual, labeled cells at micron resolution in the frontal temporal lobe.

1R01NS105820-01A1(Fischl) 12/01/18-11/30/23 1.42 cal
NIH-NINDS [redacted]
Segmenting Brain Structures for Neurologic Disorders
Successful completion of the proposed project will greatly increase the number of structures and level of detail of publicly available segmentation tools. These new capabilities will enable other studies to significantly

increase their ability to detect disease effects in research settings as well as phase II and phase III clinical trials.

(R01AG059011-01A1 (Jacques/Miller) 04/01/19-03/31/24 0.60 cal
NIH/NIA/Tufts University
[redacted]
Vitamin B12 status, cognitive decline and incident dementia
The major goals of this project are, we will analyze the scans that are of sufficient quality from 600 subjects who had FHS MRI scans from 2005-2011 and a follow-up scan from 2011-2016 that are of sufficient quality to yield interpretable results. For each of these scans we will apply our standard volumetric analysis as well as segment hippocampal subfields and apply longitudinal analysis tools. Finally, we will perform extensive quality control on the resulting morphometric measures using custom-built in-house tools capable of facilitating visual inspection of these large sized datasets
Role: Co-Investigator

PENDING

[redacted]

[redacted]

OVERLAP

If the pending grants are awarded, Dr. Fischl will work with MGH Administrators to adjust his efforts as follows so as not to exceed 12 calendar months:

5R01NS083534-05 Fischl - Dr. Fischl will reduce his effort from .96 to .12 cal months
5R01EB019956-04 Fischl - Dr. Fischl will reduce his effort from 1.92 to 1.04 cal months

There is no scientific overlap.

OTHER SUPPORT

Nicholas J. Schmansky

Commons ID: [redacted]

ACTIVE

R42 CA183150-03 (PD/PI: Wighton, van der Kouwe) NIH-NCI 04/01/2018 - 3/31/2020 2.4 cal.
AutoRegister: A System For Enhancing Accuracy of Tumor Change Detection
A project to develop a software system allowing accurate real-time registration of MR images of the brain such that the error introduced by varying head placement does not effect the measurement of the size of a tumor.

R44 NS089090-03 (**PD**/PI: **Schmansky**, Fischl) NIH-NINDS 09/01/2017 - 08/31/2019 9.6 cal.
MRI brain morphometry for computer-aided detection of neurological disorders
In this project we seek to (1) integrate novel deep-learning and Random Forest-based patch-matching image synthesis technology into FreeSurfer to make it robust to variations in scanner platform and acquisition parameters, (2) use modern parallel-processing to reduce execution time to a clinically-feasible length, and (3) develop the code in an FDA compliant manner.

PENDING

[redacted]

OVERLAP

There is no scientific overlap. To accommodate the effort required for grant R42 AG062026-01A1, effort will be reduced in grant R44 NS089090-03.

OTHER SUPPORT

Lee Tirrell

Commons ID: [redacted]

ACTIVE

R42 CA183150-03 (PD/PI: Wighton, van der Kouwe) NIH-NCI 04/01/2018 - 3/31/2020 1.2 cal.
AutoRegister: A System For Enhancing Accuracy of Tumor Change Detection
A project to develop a software system allowing accurate real-time registration of MR images of the brain such that the error introduced by varying head placement does not effect the measurement of the size of a tumor.

R44 NS089090-03 (PD/PI: Schmansky, Fischl) NIH-NINDS 09/01/2017 - 08/31/2019 10.8 cal.
MRI brain morphometry for computer-aided detection of neurological disorders
In this project we seek to (1) integrate novel deep-learning and Random Forest-based patch-matching image synthesis technology into FreeSurfer to make it robust to variations in scanner platform and acquisition parameters, (2) use modern parallel-processing to reduce execution time to a clinically-feasible length, and (3) develop the code in an FDA compliant manner.

PENDING

[redacted]

OVERLAP

There is no scientific overlap. To accommodate the effort required for grant R42 AG062026-01A1, effort will be reduced in grant R44 NS089090-03.