PI: **Chow, Ho Ming**	Title: Neural Markers of Persistence and Recovery from Childhood Stuttering: An fMRI Study of Continuous Speech Production	
Received: 02/23/2016	FOA: PAR16-057	Council: 10/2016
Competition ID: FORMS-C	FOA Title: NIDCD EARLY CAREER RESEARCH (ECR) AWARD (R21)	
1 R21 DC015853-01	Dual:	Accession Number: 3911289
IPF: 1506502	Organization: [redacted]	
Former Number:	Department: Psychiatry	
IRG/SRG: CDRC	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N	New Investigator: Early Stage Investigator:
Senior/Key Personnel:	*Organization:*	*Role Category:*
Ho Ming Chow	[redacted]	PD/PI
Allen Braun	NIH	Consultant
Soo-Eun Chang	[redacted]	Co-Investigator
Nan Ratner	University of Maryland	Co-Investigator

OMB Number 4040-0001
Expiration Date 06/30/2016

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

b. Agency Routing Number

2. DATE SUBMITTED

Application Identifier 16-PAF04924

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION

Organizational DUNS*: [redacted]

Legal Name*: [redacted]
Department:
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]

Person to be contacted on matters involving this application
Prefix: Ms. First Name*: Colleen Middle Name: L Last Name*: Vogler Suffix:
Position/Title: Project Representative
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: Email: [redacted]

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

7. TYPE OF APPLICANT* H: Public/State Controlled Institution of Higher Education

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*
Neural Markers of Persistence and Recovery from Childhood Stuttering: An fMRI Study of Continuous Speech Production

12. PROPOSED PROJECT

Start Date* 09/01/2016
Ending Date* 08/31/2019

13. CONGRESSIONAL DISTRICTS OF APPLICANT
[redacted]

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Ho Ming Middle Name: Last Name*: Chow Suffix:
Position/Title: Research Investigator
Organization Name*: [redacted]
Department: Psychiatry
Division: Medical School
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]
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: Mr. First Name*: Craig Middle Name: Last Name*: Reynolds Suffix:
Position/Title*: Director
Organization Name*: [redacted]
Department: Research & Sponsored Projects
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: Email*: [redacted]

Signature of Authorized Representative*
Craig.Reynolds

Date Signed*
02/23/2016

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:CoverLetter.pdf

424 R&R and PHS-398 Specific Table Of Contents

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: [redacted]
Duns Number: [redacted]
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]
Project/Performance Site Congressional District*: [redacted]

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Maryland
DUNS Number: [redacted]
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]
Project/Performance Site Congressional District*: [redacted]

File Name

Additional Location(s)

Funding Opportunity Number: PAR-16-057. Received Date: 2016-02-23T15:48:23.000-05:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ○ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ● No

If YES, check appropriate exemption number: ___ 1 ___ 2 ___ 3 ___ 4 ___ 5 ___ 6

If NO, is the IRB review Pending? ● **Yes** ○ **No**

IRB Approval Date:

Human Subject Assurance Number 00004969

2. Are Vertebrate Animals Used?* ○ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	ProjectSummary.pdf
8. Project Narrative*	Project_Narrative_v3.pdf
9. Bibliography & References Cited	Bibliography_Reference.pdf
10.Facilities & Other Resources	FacilitiesAndOtherResources.pdf
11.Equipment	
12. Other Attachments	AuthenticationOfKeyBiologicalChemicalResources pdf

Funding Opportunity Number: PAR-16-057. Received Date: 2016-02-23T15:48:23.000-05:00

Although symptoms of childhood stuttering fully manifest during overt, continuous speech production, little is known about the neural processes associated with speech production in children, and how these processes are disrupted, resulting in the overt manifestation of stuttering instances. Moreover, the majority of children who stutter recover naturally, but we do not know how children's brains functionally adapt to cope with the disorder and achieve fluent speech. Absent such knowledge, the neurological deficits underlying stuttering and how the disorder resolves itself cannot be fully understood, a difficulty that limits our ability to develop advances in clinical assessment and intervention. Our *long-term goal* is to develop effective therapeutic interventions to treat and prevent persistent stuttering during childhood. The *objective* of the present application, which is the next step in pursuing that goal, is to determine brain activity patterns associated with continuous speech production in children with persistent (pCWS) and children who recovered from stuttering (rCWS). The *central hypothesis* of the application is that persistent stuttering is associated with anomalous brain activity in the neural circuits for speech-motor control, while recovery from stuttering is associated with greater involvement of right frontal areas. The *rationale* of this proposed research is that an empirically-based understanding of brain activity patterns associated with continuous speech production of pCWS and rCWS is foundational for the development of future therapeutic interventions attempting to modify anomalous activity. Using a novel fMRI technique, we will test our central hypothesis by pursuing the following *specific aims*: 1) Identify brain activity associated with continuous speech production that characterizes persistent stuttering, and 2) Identify brain activity associated with continuous speech production that characterizes recovery from stuttering. To achieve Aim #1, brain activity associated fluent speech production between pCWS and controls will be compared. Furthermore, brain activity associated with fluent and stuttered speech production in pCWS will be separated and compared. To achieve Aim #2, brain activity associated with fluent speech production between rCWS and controls will be compared. This application is *innovative* because it will be the first study to examine both cortical and subcortical activity associated with continuous speech production in children with high spatial resolution using a novel fMRI de-noising technique. Findings of this project will be *significant* because they are expected to fundamentally advance our understanding of the neural processes associated with fluent and disfluent continuous speech production in children who stutter and provide insights into neuroplasticity associated with recovery from childhood stuttering. Ultimately, this new knowledge may guide the future development of better treatment strategies for childhood stuttering.

Project Narrative

The proposed studies address an important and under-investigated area of childhood developmental stuttering that is relevant to the mission of NIDCD. Findings of these studies are expected to advance our understanding of the neural processes associated with fluent and disfluent continuous speech production in children who stutter and provide insights into neuroplasticity associated with recovery from childhood stuttering. This new knowledge may guide the development of more effective treatment strategies for childhood stuttering.

FACILITIES AND RESOURCES

[redacted]

This project has access to the state-of-the-art functional magnetic imaging (fMRI) equipment and research resources to successfully accomplish the objectives outlined in our proposal. The fMRI laboratory involved in data collection is located in the North Campus of the [redacted], near the Department of Psychiatry at the [redacted]. The fMRI laboratory has participant-dedicated parking spaces, and is connected by high-speed networks to laboratories on the campuses of the [redacted]. The fMRI laboratory is decorated in a child-friendly way and the staff is experienced in pediatric neuroimaging.

The [redacted] fMRI Laboratory

The fMRI laboratory is equipped with two state-of-the-art 3.0T GE MRI scanners (MR750, DV25.0 software version). They both have high performance gradient systems (peak 50 mT/m, slew rate 200 T/m/s). This model has a full set of functional imaging capabilities, including single-shot imaging (spiral and EPI), automated shimming, real-time image reconstruction and processing. This project will use a standard eight-channel coil for parallel imaging, but two 32-channel receive arrays from Nova Medical are available for greater image acquisition speed-up factors and improved SNR, and implementation of cutting-edge multi-band acquisitions. The latest version (FOMRI-III) of noise cancellation optical microphone from OptoAcoustic (Moshav Mazor, Israel) and 2 MRI compatible cameras from MRC Systems (Heidelberg, Germany) are available for recording participants' audio and video during speech production. Two large scale Linux servers with dedicated backup are available for reconstruction, processing and archival storage (Main machine: 24 core/16G RAM/15T storage; secondary machine: 8 core/16G/5T). Software packages available for data collection and analysis include EPrime, Presentation, MATLAB, SPM12, FSL, AFNI, C++ and a variety of custom packages. A patient waiting room and examination rooms are available in the fMRI laboratory. Two mock scanners at nearby locations are available for pediatric participant to get familiar with the scanning environment.

Speech Neurophysiology Laboratory at the [redacted]

Dr. Soo-Eun Chang, the co-I of this project, has offered the PI the use of her laboratory's equipment for fMRI data analysis for the proposed project. The Speech Neurophysiology Laboratory is designed for conducting multimodal imaging data and advanced data analysis. The laboratory is equipped with a Linux server with 16 cores, 32G RAM and 12T storage dedicated for MRI data analyses and backup. Software packages available for data and statistical analysis include MATLAB, R, SPM, FSL, AFNI and SPSS. In addition to hardware, the laboratory has built up a database of about 70 children with developmental stuttering (comprising persistent and recovered children) and 70 typically developing children who are interested in participating neuroimaging research. Dr. Chang and her team have created an effective work flow for subject recruitment, screening and visit scheduling. The laboratory's participant pool and staff experience with pediatric research greatly enhance the chances for success of this project.

Department of Psychiatry, the [redacted]

The Department of Psychiatry will provide necessary facilities and support to personnel involved with this project at Rachel Upjohn Building. These facilities include office space, furnishings, telephone, desktop computer, internet connection and other commonly used office and research utilities. Shared facilities of the Department include two interview and testing rooms, a 'mock fMRI scanner' facility, printing and fax machine. Moreover, the Department of Psychiatry has funded a core facility to provide hardware and software support necessary to analyze neuroimaging data (PET, MRI, fMRI). It is fully equipped with latest releases of statistical parametric mapping (SPM12) and BrainVoyager software packages and uses a networked cluster of Linux

workstations. This group provides intellectual support for study design, analysis, statistics and interpretation across platforms, and periodically requires license renewals, hardware upgrades and parts replacements.

Scientific Environment

The environment in which the proposed research will take place is perfectly suited to ensure success. The PI holds a research faculty position at the Department of Psychiatry. His position is fully supported through a combination of departmental and private foundation funding and is totally dedicated to stuttering research. Collaborating with the co-I Dr. Chang's Speech Neurophysiology Laboratory, which has been conducting the largest longitudinal neuroimaging research of childhood stuttering in the last five years, the PI has been involved in various aspects of stuttering research. This collaboration is an important part of this proposal because it provides an environment to synergize Dr. Chang's experience in conducting pediatric neuroimaging research in stuttering and the PI's expertise in advanced neuroimaging technologies. Moreover, Department of Psychiatry at the university provides a simulating intellectual environment and perspectives from childhood development and developmental disorders to foster new ideas on stuttering research.

The [redacted] Research Capacity

The [redacted] is a nationally-recognized research and academic institution, which provides a wide range of resources to investigators to lead novel research. These resources include comprehensive library collections and databases, technological and statistical expertise, inter-disciplinary collaboration and training, state-of-the art facilities, and a wireless-enabled campus. Collectively, these resources provide the capacity for success of the proposed project. The [redacted] ranks as one of the leading medical centers in the U.S. The [redacted] are situated on an 84-acre campus in [redacted]. A major mission of the [redacted] is to foster academic research; its success has been reflected in major contributions to both basic and clinical sciences, in national recognition accorded to its faculty, and in levels of outside funding won for research initiatives. In the NIH fiscal year 2014, The [redacted] received [redacted] ranking twelfth among U.S. public medical schools nationwide in total NIH funding. UMHS is the 4th largest teaching hospital in the country according to Modern Healthcare magazine, and [redacted] is highly ranked across a broad range of fields including health, medicine, science, engineering, business, and law.

UNIVERSITY OF MARYLAND

Ratner Office and Lab Facilities:

Dr. Ratner has both an office and a dedicated laboratory area with a total of nine computer stations. All computers are networked to both the University of Maryland as well as a separate college system that provides and maintains programs for email, word processing, statistical analysis and other commonly used office and research utilities. The College of Behavioral & Social Sciences also maintains two distance learning classrooms which have already been used to conduct CLAN training sessions with laboratories (PI's and other faculty at the University of Michigan) via two-way video hookup. As a consultant to the TalkBank project, [redacted] Dr. Ratner maintains close and frequent contact with its PI (Dr. Brian MacWhinney) and primary programmer (Leonid Spektor); this has historically allowed her the ability to contribute to program development that is specifically useful to individual researchers, such as the PI, and to obtain immediate assistance for technological difficulties or desired changes to computational utilities. Dr. Ratner has the assistance of two Research Assistants, funded through general University funds, as well as a large number of undergraduate research volunteers who participate in her lab activities via the very active Maryland Center for Undergraduate Research (MCUR); the MCUR is one of a number of campus activities that emphasizes the importance of research training for its undergraduates. Dr. Ratner also works within the larger

local community of fluency researchers, such as Drs. Allen Braun and Dennis Drayna at NIDCD Intramural, and Dr. Shelley Brundage at George Washington University. This engagement provides opportunities to discuss and interpret research findings.

Scientific Environment

The Department of Hearing and Speech Science (HESP), University of Maryland and surrounding area has a strong presence in multiple areas of communication sciences and disorders: hearing/perception (e.g., Drs. Rochelle Newman, Samira Anderson, Matthew Goupell, & Sandra Gordon-Salant in HESP), neurogenic speech and language disorders (Yasmeen Shah, Jared Novick and Nancy Pearl Solomon in HESP) and developmental language research (e.g., Yi Ting Huang in HESP; Drs. Jeffrey Lidz and Naomi Feldman in Linguistics; Drs. Nathan Fox, D. J. Bolger, and Geetha Ramani in Human Development; Drs. Tracy Riggins, Jonathan Beier, and Elizabeth Redcay in Psychology). HESP also has as faculty an ASHA Fellow (Vivian Sisskin, nationally known and awarded for her clinical expertise in stuttering). Finally, the University of Maryland is home to the largest and most integrated community of language scientists in North America through the Maryland Language Science Center (**http://languagescience.umd.edu**), including researchers from 17 departments, programs and affiliated centers and institutes (including the Center for Advanced Study of Language, the National Foreign Language Center, the University of Maryland Institute for Advanced Computer Studies, the Maryland Neuroimaging Center, and the Institute for Systems Research).

The University of Maryland Research Capacity

The University of Maryland offers a number of cross- disciplinary research groups that provide venues for the sharing of research findings and consultation. Its program in Neuroscience and Cognitive Science (NACS), the Developmental Science Field Committee, the University of Maryland Autism Research Consortium (UMARC), and the Center for the Comparative and Evolutionary Biology of Hearing all meet and share research updates frequently. The University of Maryland has also just announced the formation of the Maryland Language Science Center, which will add further to the scientific richness of the local research community. Several of these groups have their own colloquium series, which bring in outside members of the scientific community to meet with Maryland faculty. Maryland is thus an ideal location for work in communication sciences and disorders.

Authentication of Key Biological and/or Chemical Resources

None

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Ho Ming Middle Name Last Name*: Chow Suffix:

Position/Title*: Research Investigator
Organization Name*: [redacted]
Department: Psychiatry
Division: Medical School
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: PD/PI Other Project Role Category:

Degree Type: PhD Degree Year: 2008

	File Name
Attach Biographical Sketch*:	Biosketch_Chow.pdf
Attach Current & Pending Support:	

Tracking Number: GRANT12102741 Funding Opportunity Number: PAR-16-057 . Received Date: 2016-02-23T15:48:23.000-05:00

PROFILE - Senior/Key Person

Prefix: First Name*: Allen Middle Name Last Name*: Braun Suffix:

Position/Title*: Cheif, Language Section, NIDCD
Organization Name*: NIH
Department:
Division: NIDCD
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: E-Mail*: [redacted]

Credential, e.g., agency login:

Project Role*: Consultant Other Project Role Category:

Degree Type: MD Degree Year: 1980

File Name
Attach Biographical Sketch*: Biosketch_Braun.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Soo-Eun Middle Name Last Name*: Chang Suffix:

Position/Title*: Research Professor
Organization Name*: [redacted]
Department: Psychiatry
Division: Medical School
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: E-Mail*: [redacted]

Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PhD Degree Year: 2005

File Name
Attach Biographical Sketch*: Biosketch_Chang.pdf
Attach Current & Pending Support:

Tracking Number: GRANT12102741 Funding Opportunity Number: PAR-16-057 . Received Date: 2016-02-23T15:48:23.000-05:00

PROFILE - Senior/Key Person

Prefix: First Name*: Nan Middle Name Last Name*: Ratner Suffix:

Position/Title*: Professor
Organization Name*: University of Maryland
Department: Hearing and Speech Sciences
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: E-Mail*: [redacted]

Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Ed.D Degree Year: 1982

	File Name
Attach Biographical Sketch*:	Bioshetch_Ratner.pdf
Attach Current & Pending Support:	

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Chow, Ho Ming

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

POSITION TITLE: Research Investigator

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Hong Kong	BENG	12/1997	Industrial Engineering
University of Hong Kong	MPHIL	11/2000	Ergonomics
University of Osnabrueck	PHD	11/2008	Cognitive Science
NIDCD/NIH	Postdoctoral Fellow	03/2014	Neuroscience/Neuroimaging

A. Personal Statement

With a background in cognitive neuroscience, psycholinguistics, engineering, I have been able to develop and test cutting edge brain imaging techniques to study the neurobiology of human communication. I am particularly interested in understanding the neural mechanisms of speech production and how these mechanisms are disrupted, leading to speech disorders. During the first 3 years (2009-2012) of my postdoctoral training at the NIH, my research focused on studying discourse-level language comprehension and production in healthy volunteers. Additionally, I was actively involved in the entire process of developing a novel technique to remove speech-related artifacts from fMRI signals (Xu et al., 2014). With the capability to use fMRI to examine brain activity associated with continuous speech, in 2012, I started a comprehensive research project to study functional and structural anomalies in the brains of adults who stutter (n = 36 adults who stutter and 30 matched controls). I led, designed, and implemented this project that included i) three fMRI experiments to study word-, sentence-, discourse-level production, ii) diffusion tensor imaging to study white-matter structural anomalies, and iii) genetic sequencing to study potential relationship between stuttering-related mutation and brain anomalies. The first paper associated with this stuttering project has just been published (Drayna et al, 2015) and several other manuscripts are in preparation. I am confident that my technical expertise in neuroimaging and experience in empirically studying stuttering combined with demonstrated collaboration with Dr. Chang (since 2015) and Dr. Ratner (since 2013) will significantly contribute to the success of the proposed project. For this current project, I will meet weekly with Dr. Chang, Dr. Ratner (via videoconferencing) and the research assistant to review project progress. I will be overseeing all aspects of this research, including participant recruitment, fMRI data acquisition, data analysis and interpretations. I expect that successful completion of the proposed research will contribute critical elements in understanding the neural characteristics of persistence and recovery from childhood stuttering.

1. Xu Y, Tong Y, Liu S, Chow HM, AbdulSabur NY, Mattay GS, Braun AR. Denoising the speaking brain: toward a robust technique for correcting artifact-contaminated fMRI data under severe motion. Neuroimage. 2014 Dec;103:33-47. PubMed PMID: 25225001; PubMed Central PMCID: PMC4312243.

2. Drayna D, Raza M, Domingues C, Webster R, Sainz E, Paris E, Rahn R, Gutierrez J, Chow HM, Mundorff J, Kang C, Riaz N, Khan S, Basra A, Braun A, Riazuddin S. Mucolipidosis Types II and III and non-syndromic stuttering are associated with different variants in the same genes. Eur J Hum Gent. PMID: 26130485

B. Positions and Honors

Positions and Employment

2009 - 2014 Postdoctoral Research Fellow, NIDCD/NIH, Bethesda, MD
2014 - 2015 MRI Psychology Researcher, NIDCD/NIH through Kelly Services, Inc, Bethesda, MD
2015 - Research Investigator, [redacted]

Other Experience and Professional Memberships

Honors

1997-1999 Postgraduate Studentship, University of Hong Kong
2005-2008 Research Grants for Doctoral Candidates and Young Academics and Scientists, DAAD (German Academic Exchange Service)
2008 Travel Award, Organization of Human Brain Mapping
2009-2014 Visiting Fellow Award, National Institutes of Health
2015 Fellows Award for Research Excellence, National Institutes of Health
2015 Meritorious Poster Award, American Speech-Language-Hearing Association (ASHA)

C. Contribution to Science

1. **Developing an fMRI procedure to study continuous speech**. I was actively involved in developing an effective and flexible de-noising technique to overcome the severe image distortion caused by overt speech artifacts during fMRI scanning. These artifacts are primarily related to the interaction between various motion effects and the magnetic fields employed by fMRI. Our denoising technique has been validated with positron emission tomography (an imaging technique much less susceptible to the above artifacts) and demonstrated to perform better than other state-of-the-art de-noising methods. This novel method opens new research horizons in studying neural processes of speech production and speech disorders using fMRI. In close collaboration with the project leader (Y. Xu), I was involved in developing and testing possible fMRI de-noising strategies, and applying the final de-noising procedures to evaluate its effectiveness.

    a. AbdulSabur NY, Xu Y, Liu S, Chow HM, Baxter M, Carson J, Braun AR. Neural correlates and network connectivity underlying narrative production and comprehension: a combined fMRI and PET study. Cortex. 2014 Aug;57:107-27. PubMed PMID: 24845161.
    b. Xu Y, Tong Y, Liu S, Chow HM, AbdulSabur NY, Mattay GS, Braun AR. Denoising the speaking brain: toward a robust technique for correcting artifact-contaminated fMRI data under severe motion. Neuroimage. 2014 Dec;103:33-47. PubMed PMID: 25225001; PubMed Central PMCID: PMC4312243.

2. **Studying sensorimotor involvement with language comprehension.** Findings from our recent empirical studies suggest that in addition to the left perisylvian language regions, sensorimotor areas are also involved in language comprehension. Results indicate that the activity of sensorimotor areas and their functional connectivity with the left language regions are associated with the processing of semantic content. Moreover, functional connectivity within sensorimotor areas is modulated by the comprehenders' personal experience. These findings indicate that comprehension should be viewed as a mental simulation of personal experience.

    a. Chow HM, Kaup B, Raabe M, Greenlee MW. Evidence of fronto-temporal interactions for strategic inference processes during language comprehension. Neuroimage. 2008 Apr 1;40(2):940-54. PubMed PMID: 18201911.
    b. Chow HM, Mar RA, Xu Y, Liu S, Wagage S, Braun AR. Embodied comprehension of stories: interactions between language regions and modality-specific neural systems. J Cogn Neurosci. 2014 Feb;26(2):279-95. PubMed PMID: 24047383.

c. Chow HM, Mar RA, Xu Y, Liu S, Wagage S, Braun AR. Personal experience with narrated events modulates functional connectivity within visual and motor systems during story comprehension. Hum Brain Mapp. 2015 Apr;36(4):1494-505. PubMed PMID: 25545633.

3. **Studying creative use of language**. We use fMRI to study brain activity associated with lyrical improvisation during freestyle rap, and generation and revision of poetry. We demonstrate that, in both art forms, creative processes are associated with the deactivation of lateral prefrontal areas that play an important role in executive control.

d. Liu S, Chow HM, Xu Y, Erkkinen MG, Swett KE, Eagle MW, Rizik-Baer DA, Braun AR. Neural correlates of lyrical improvisation: an FMRI study of freestyle rap. Sci Rep. 2012;2:834. PubMed PMID: 23155479; PubMed Central PMCID: PMC3498928.

e. Liu S, Erkkinen MG, Healey ML, Xu Y, Swett KE, Chow HM, Braun AR. Brain activity and connectivity during poetry composition: Toward a multidimensional model of the creative process. Hum Brain Mapp. 2015 May 26. PubMed PMID: 26015271.

4. **Multimodal imaging and functional connectivity.** Using simultaneous acquisition of EEG and fMRI, my former colleagues and I discovered that the connectivity patterns in different sleep stages of humans change dramatically. Comparing rapid eye movement (REM) sleep with slow-wave sleep as well as wakeful rest, we demonstrated that REM sleep is characterized by temporally dynamic interactions between unimodal sensorimotor areas and the higher-order association cortices. We speculated that these interactions in important for dreaming and memory consolidation.

a. Chow HM, Horovitz SG, Carr WS, Picchioni D, Coddington N, Fukunaga M, Xu Y, Balkin TJ, Duyn JH, Braun AR. Rhythmic alternating patterns of brain activity distinguish rapid eye movement sleep from other states of consciousness. Proc Natl Acad Sci U S A. 2013 Jun 18;110(25):10300-5. PubMed PMID: 23733938; PubMed Central PMCID: PMC3690889.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/ho%20ming.chow.1/bibliography/48036263/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

none

Completed Research Support

2009/04/02 - 2015/01/16
1ZIADC000031, NIDCD/NIH Intramural Research Program
Braun, Allen (PI)
Functional Neuroimaging Studies in Humans
The aim of this project is to use multimodal imaging techniques to characterize brain activation patterns associated with language comprehension and production in normal subjects and individuals with neurological disorders affecting human communication. My major contribution to this project is to investigate functional roles of sensorimotor areas in language comprehension, and functional/anatomical brain anomalies associated with developmental stuttering.
Role: Co-Investigator

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Allen Richard Braun, M.D.

eRA COMMONS USER NAME (agency login):

POSITION TITLE: Chief, Language Section, NIDCD, NIH

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Washington University, St. Louis	BA	1964 - 1968	English Lit/Biology
University of Wisconsin, Madison		1974- 1976	Neuroendocrinology
Rush Medical College, Chicago	MD	1976 - 1980	Medicine
Rush, Pres St. Luke's, Chicago		1981 - 1984	Neurology Residency
NIH Clinical Center, Bethesda		1986 - 1988	Nuc Med Residency

A. Personal Statement

My primary research interest is in understanding how language is instantiated in the brain, how brain-language relationships are interrupted by disorders that affect the ability to communicate, and how these disorders can be treated. To pursue these goals, my lab recently developed an fMRI de-noising technique, which has been demonstrated to be able to remove artifacts related to overt, continuous speech production from functional magnetic resonance images (Xu et al., 2014). This technique allows us to examine brain activity during continuous speech production using fMRI, which was not considered feasible in the past. The ability to study brain activity associated with continuous speech is extremely important because this is the context in which symptoms of speech disorders such as development stuttering fully emerge. Because I oversaw the team, in which Dr. Chow was a key member, that developed this de-noising technique, I am well suited to support the research studies Dr. Chow proposes to use this technique to study children who stutter. I am excited that Dr. Chow is planning to use this method to investigate this important but unexplored topic and look forward to the collaboration.

1. Xu Y, Tong Y, Liu S, Chow HM, AbdulSabur NY, Mattay GS, Braun AR. Denoising the speaking brain: toward a robust technique for correcting artifact-contaminated fMRI data under severe motion. Neuroimage. 2014 Dec;103:33-47. PubMed PMID: 25225001; PubMed Central PMCID: PMC4312243.

B. Positions and Honors

Positions and Employment

1984 - 1986 Medical Staff Fellow, Experimental Therapeutics Branch, NINDS/NIH
1986 - 1988 Senior Staff Fellow, Department of Nuclear Medicine, Clinical Center, NIH
1988 - 1991 Head, Nuclear Medicine Unit, Clinical Brain Disorder Branch, NIMH/NIH
1991 - 1994 Medical Officer, Voice and Speech Section, NIDCD/NIH
1994 - 2003 Acting Chief, Language Section, NIDCD/NIH
2003 - Chief, Language Section, NIDCD/NIH

Other Experience and Professional Memberships

Additional Professional Activities:
Associate Editor, Human Brain Mapping
Editorial Board, Journal of Fluency Disorders
Adjunct Associate Professor, Neuroscience, Cognitive Science, University of MD

Medical Staff (Research), Suburban Hospital, Bethesda, MD
NIH Central Tenure Committee
NIH MRI Steering Committee
NIH Positron Emission Tomography Steering Committee
NIH Imaging Probe Development Steering Committee
NIH Mouse Imaging Facility Steering Committee
Howard Hughes Medical Institute Scholars Advisor
NIH LCOM Study Section, 2003, 2005
NIH Pharmacy and Therapeutics Committee, 1995-2001
NIDCD-NINDS Institutional Review Board, 1995-2002
Chairman, Radiation Safety Committee, NIMH Neuroscience Center, 1988-1991
Chairman, Radioactive Drug Research Committee, NIMH Neuroscience Center 1988-1991

Board Certification:

National Board of Medical Examiners, 1981
American Board of Psychiatry and Neurology (Neurology), 1987
American Board of Nuclear Medicine, 1993

Professional Affiliations:

American Academy of Neurology Society of Nuclear Medicine Society for Neuroscience Cognitive Neuroscience Society

Honors

1998	Merit Award (NIDCD) "For innovative and insightful research contributions on neuroimaging relevant to communication disorders"
1999	Special Act of Service Award (NIDCD)
1999	Staff Recognition Award
1999	Special Act of Service Award (EEO)
2000	Staff Recognition Award
2004	Special Act of Service Award (NIDCD)
2013	Plenary Address, DC Speech and Hearing Association Annual Meeting

C. Contribution to Science

1. SLEEP: Used both Positron Emission Tomography and Magnetic Resonance Imaging Methods to characterize patterns of cerebral activity during the sleep wake cycle. This research documented a novel set of findings centered on robust changes in frontal lobe activity that have proved to be foundational in the field.

    a. Braun AR, Balkin TJ, Wesensten NJ, Varga M, Baldwin P, Carson RE, Belenky G, Herscovitch P. Regional Cerebral Blood Flow Throughout the Sleep-Wake Cycle: An H2O-15 Positron Emission Tomography Study. Brain, 120:1173-1197, 1997. PMID: 9236630

    b. Braun AR, Balkin TJ, Wesensten NJ, Gwadry F, Varga M, Baldwin P, Carson RE, Belenky G, Herscovitch P. Dissociated pattern of activity in visual cortices and their projections during human rapid eye movement sleep. Science, 279:91-95, 1998. PMID: 9417032

    c. Balkin T, Braun AR, Wesensten N, Jeffries K, Varga M, Baldwin P, Belenky G, Herscovitch, P. The Process of Awakening: A PET Study of Regional Brain Activity Patterns Mediating the Reestablishment of Alertness and Consciousness. Brain, 125: 2308-2319, 2002. PMID: 12244087

    d. Chow HM, Horovitz SG, Carr WS, Picchioni D, Coddington N, Fukunaga M, Xu Y, Balkin TJ, Duyn JH, Braun AR. Rhythmic alternating patterns of brain activity distinguish rapid eye movement sleep from other states of consciousness. Proc Natl Acad Sci., 110(25), 2013. PMID: 23733938

2. DISCOURSE: Conducted a series of neuroimaging studies that characterized brain activity during naturalistic discourse level language use. Early studies demonstrated engagement of a host of regions extending beyond the perisylvian language cortices during real-world language use. Later studies better characterized interactions between language and other cognitive and sensorimotor systems during comprehension and production of discourse.

a. Braun AR, Guillemin A, Hosey L, Varga M. The neural organization of discourse: an H2 15O-PET study of narrative production in English and American sign language. Brain 124: 2028-2044, 2001. PMID: 11571220

b. AbdulSabur NY, Xu Y, Liu S, Chow HM, Braun AR. Neural correlates and network connectivity underlying narrative production and comprehension: a combined fMRI and PET study Cortex. 57:107-27, 2014. PMID: 24845161

c. Chow HM, Mar RA, Xu Y, Liu S, Wagage S, Braun AR. Embodied comprehension of stories: Interactions between language regions and modality-specific neural systems. Journal of Cognitive Neuroscience. 26(2):279-95, 2014. PMID: 24047383

d. Chow HM, Mar RA, Xu Y, Liu S, Wagage S, Braun AR. Personal experience with narrated events modulates functional connectivity within visual and motor systems during story comprehension. Hum Brain Mapp. 36(4):1494-505, 2015. PMID: 25545633

3. LANGUAGE EVOLUTION: A series of studies in humans and non-human primates provided data suggesting a plausible model for language evolution. Early studies demonstrate structural and functional similarities in perisylvian cortices that appear to support species specific communication in human and non-human primates. Later studies in humans provided data that are consistent with a gestural origins model.

a. Gannon PJ, Holloway RL, Broadfield DC, Braun AR. Asymmetry of Chimpanzee Planum Temporale: Humanlike Pattern of Wernicke's Brain Language Area Homolog. Science, 279: 220-222, 1998. PMID: 9422693

b. Gil-da-Costa R, Braun A, Lopes M, Hauser MD, Carson RE, Herscovitch P, Martin A. Towards an evolutionary perspective on conceptual representation: Species-specific calls activate visual and affective processing systems in the macaque. Proc Natl Acad Sci USA, 101:17516-17521, 2004. PMID: 15583132

c. Gil-da-Costa R., Martin A., Lopes M., Munoz, M., Fritz JB, Braun, A.R. Species-specific calls activate homologues of Broca's and Wernicke's areas in the macaque. Nat Neurosci 9(8):1064-70, 2006. PMID: 16862150

d. Xu J, Gannon PJ, Emmorey K, Smith JF, Braun AR. Symbolic Gestures and Spoken Language are Processed by a Common Neural System. PNAS 106:20664-20669, 2009. PMID: 19923436

4. CREATIVITY: An ongoing series of studies is designed to provide support for a multidimensional model of creativity, accounting for multiple stages of the creative process, audience responses to a creative product and the impact of expertise. Early studies examined musical improvisation, later studies focus on linguistic creativity.

a. Limb CJ, Braun AR. Neural Substrates of Spontaneous Musical Performance: A Functional Neuroimaging Study of Jazz Improvisation PLoS One 3(2): e1679, 2008. PMID: 18301756

b. Liu S, Chow HM, Xu Y, Erkkinen MH, Swett KE, Engle MW, Rizik-Baer DA, Braun AR. Neural correlates of lyrical improvisation: An fMRI Study of Freestyle Rap. Sci Rep. 2(834), 2012. PMID: 23155479

c. Liu S, Erkkinen MG, Healey ML, Xu Y, Swett KE, Chow HM, Braun AR. Brain Activity and Connectivity during Poetry Composition: Toward a Multi-dimensional Model of the Creative Process. Hum Brain Mapp. 36(9), 2015. PMID: 26015271

5. BASAL GANGLIA AND LANGUAGE: Used functional neuroimaging and behavioral methods to examine abnormalities of speech-language processing in neurological disorders characterized by abnormalities of the extrapyramidal system. Each of these studies strongly implicates the basal ganglia in the language phenotype characteristic of these disorders.

a. Braun AR, Stoetter B, Randolph C, Hsiao J, Vladar K, Gernert J, Carson RE, Herscovitch P, Chase TN. The Functional Neuroanatomy of Tourette Syndrome: An FDG PET study. I. Regional Changes in

Glucose Metabolism Differentiating Patients and Controls. Neuropsychopharmacology, 9:277-291, 1993. PMID: 8597526

b. Braun AR, Varga M, Stager S, Shulz G, Selbie S, Maisog JM, Carson RE, Ludlow CL. Altered Patterns of Cerebral Activity During Speech and Language Production in Developmental Stuttering. An H2O-15 Positron Emission Tomography Study. Brain, 120:761-784, 1997. PMID: 9183248

c. So A, Thomasen M, Schulz GM, Guillemin A, Hosey L, Varga M, Ludlow CL, Braun AR. Alterations in CNS Activity Induced by Botulinum Toxin Treatment in Spasmodic Dysphonia: An H215O-PET Study. Journal of Speech, Language, and Hearing Research 49: 1127–1146, 2006. PMID: 17077220

d. Schulz GM, Hosey LA, Bradberry TJ, Stager SV, Lee LC, Pawha R, Lyons KE, Metman LV, Braun AR. Selective left, right and bilateral stimulation of subthalamic nuclei in Parkinson's Disease: Differential effects on motor, speech and language function. Journal of Parkinson's Disease 2(1), 29-40, 2012. PMID: 23939406

D. Research Support

Ongoing Research Support

1994-
1ZIADC000031, NIDCD/NIH Intramural Research Program
Braun, Allen (PI)
Functional Neuroimaging Studies in Humans
The aim of the project is to understand how language is instantiated in the brain, how brain-language relationships are interrupted by disorders that affect the ability to communicate, and how these disorders can be treated. We employs a combination of imaging modalities—hemodynamic methods (PET and fMRI) complemented by electrophysiological (EEG/ERP and magnetoencephalography) and PET radiochemical tracer techniques—to this end. We investigate both language production and comprehension, since disorders that affect speech and language typically have a significant impact on both, and how the brain processes language cannot be completely understood by studying either in isolation. We study language at multiple levels, from its elementary perceptual and motor features, to higher-level linguistic processing. Most importantly, I am interested in more complex, real-world language use because this ecologically valid condition is often the only context in which symptoms of many language disorders present. We are interested in a broad array of such disorders including TBI, post-stroke aphasia as well as disorders that reflect pathology at the borderland between motor and cognitive-linguistic function such as Parkinson¹s disease and developmental stuttering. In all of our clinical studies, the overarching goal is to use our methods to contribute to the design and monitor the efficacy of therapeutic interventions.

Completed Research Support

none

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Chang, Soo-Eun

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

POSITION TITLE: Assistant Professor, Rosa Casco Solano-Lopez Research Professor of Child and Adolescent Psychiatry

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Seoul National University, Seoul	BA	02/1996	Psychology
Vanderbilt University, Nashville, Tennessee	MS	08/1999	Hearing and Speech Sciences
University of Illinois at Urbana-Champaign, Champaign, Illinois	PHD	08/2005	Speech and Hearing Science
National Institute of Neurological Disorders and Stroke (NINDS) Intramural research program, NIH, Bethesda, Maryland	Postdoctoral Fellow	07/2009	Clinical Neuroscience

A. PERSONAL STATEMENT

I was trained in the field of speech and hearing sciences and have clinical certification in Speech-Language Pathology. As a result, I have had regular contact with both children and adults who stutter and have thus become very aware of the significant burden that stuttering can inflict on one's academic, emotional, social, and vocational life and because of that the deleterious impact this communication disorder has on the nation's health. In attempts to address these issues, I have devoted my research career to a better understanding of the characteristics, development and etiology of stuttering. Such knowledge, I believe, should eventually contribute to more data-based, precise diagnosis of and efficacious treatment of stuttering. This research (presently funded through an NIDCD R01 grant) currently involves a longitudinal study of sexually dimorphic brain development in children who stutter (CWS), resulting in a collection of over 280 longitudinal MRI scans and behavioral data from more than 90 children who do and do not stutter. To date, this plan of study has led to publications reporting novel and important insights into the neural bases of childhood stuttering, insights that we will continue to publish in the near future and hopefully extend beyond that with support for the proposed application.

Dr. Chow's proposed studies represent a novel and important extension of the studies that have been conducted to date in children who stutter. Capturing brain responses during overt, connected speech production with fMRI is an important new technological advance that will allow us, for the first time, to examine brain activity patterns that differ in children who stutter compared to controls during fluent and disfluent speech production. Although we have evidence of aberrant activity during these speech conditions in adults who stutter, we do not know whether these same aberrant brain activity patterns are present in children who stutter. Further, it would be important to examine whether children who have recovered from stuttering exhibit brain activity differences from children with persistent stuttering: recovered children's brain responses during fluent speech would elucidate neural mechanisms that underlie recovery, which may, in the future serve as neural targets for developmentally appropriate intervention strategies for children who stutter. I am very excited to be a part of this research and am happy to contribute to Dr. Chow's research by providing access to a relatively large pool of children with persistent stuttering as well as those who have recovered from stuttering. The longitudinal study sample that I have acquired in the last four years provide a unique opportunity for us to retroactively examine previously acquired behavioral and neuroimaging data on children who have been presently identified as persistent or recovered, allowing us to compare these data to new fMRI data during overt speech tasks.

1. Chang SE, Erickson KI, Ambrose NG, Hasegawa-Johnson MA, Ludlow CL. Brain anatomy differences in childhood stuttering. Neuroimage. 2008 Feb 1;39(3):1333-44. PubMed PMID: 18023366; PubMed Central PMCID: PMC2731627.
2. Chang SE, Zhu DC. Neural network connectivity differences in children who stutter. Brain. 2013 Dec;136(Pt 12):3709-26. PubMed PMID: 24131593; PubMed Central PMCID: PMC3859219.
3. Chang SE. Research updates in neuroimaging studies of children who stutter. Semin Speech Lang. 2014 May;35(2):67-79. PubMed PMID: 24875668.
4. Chang SE, Zhu DC, Choo AL, Angstadt M. White matter neuroanatomical differences in young children who stutter. Brain. 2015 Mar;138(Pt 3):694-711. PubMed PMID: 25619509.

B. POSITIONS AND HONORS

Positions and Employment

1998 - 1999 Research Assistant, Vanderbilt University, Nashville, TN
1999 - 2000 Research Assistant, Vanderbilt University, Nashville, TN
1999 - 2000 Clinical Fellow, Gateway Health System, Clarksville, TN
2002 - 2005 Research Assistant , University of Illinois at Urbana-Champaign, Champaign, IL
2005 - 2009 Postdoctoral Research Fellow, NINDS/NIH, Bethesda, MD
2009 - 2013 Assistant Professor, Michigan State University, Department of Communicative Sciences and Disorders, East Lansing, MI
2013 - Assistant Professor, Rosa Casco Solano-Lopez Research Professor of Child and Adolescent Psychiatry, [redacted]

Other Experience and Professional Memberships

1999 - Certified member, American Speech-Language-Hearing Association
2003 - Member, Society for Neuroscience (SfN)
2006 - Member, ASHA division 4, Fluency and Fluency Disorders
2007 - 2009 Member, Organization for Human Brain Mapping
2009 - 2010 Editorial committee member, ASHA Convention Program Sub-Committee on Fluency
2011 - Review Editor, Frontiers in Auditory Cognitive Neuroscience
2011 - Member, Korean Academy of Speech-Language Pathology and Audiology

Honors

1992 Academic scholarship, Seoul National University
1993 SK scholarship for distinguished undergraduates, SK group
2003 University of Illinois Campus Research Board grant award , University of Illinois
2005 Ehud and Jane Yairi International Student Award, Ehud Yairi
2005 ASHA student research travel award, American Speech-Language-Hearing Association (ASHA)
2006 NINDS Fellow Special Act Award, NINDS Intramural Research Program
2007 Functional Mapping of the Human Brain (OHBM) Travel Award , OHBM
2009 ASHA Lessons for Success Research Conference: Developing the Emerging Scientist , American Speech-Language-Hearing Association
2014 Endowed Professorship in Child and Adolescent Psychiatry, [redacted]
2015 Elizabeth Jane Crosby award, [redacted]

C. Contribution to Science

1. I conducted the first study examining brain anatomical differences in children who stutter, which included persistent and recovered children. This study involved group comparisons whole brain gray matter volume with voxel based morphometry (VVBM), and vowel-wise analyses of fractional anisotropy (a measure reflecting white matter integrity) with Diffusion Tensor Imaging (DTI). I designed the study, independently

obtained funding to support the study (as a graduate student, I obtained a campus internal research grant), conducted the data collection and analyses, and wrote the paper.

a. Chang SE, Erickson KI, Ambrose NG, Hasegawa-Johnson MA, Ludlow CL. Brain anatomy differences in childhood stuttering. Neuroimage. 2008 Feb 1;39(3):1333-44. PubMed PMID: 18023366; PubMed Central PMCID: PMC2731627.

2. I conducted a study using multimodal neuroimaging techniques that allowed examination of both structural and functional connectivity differences in the brains of individuals who stutter compared to a control non-stuttering group. This study showed converging evidence of a possible auditory-motor integration deficit, and an aberrant thalamus-cortical network connectivity in stuttering speakers. The task based fMRI study involved eliciting speech perception, planning, and overt production processes in normally speaking and stuttering individuals using a sparse sampling fMRI paradigm. The results revealed differences in brain activity patterns during all phases of speech processing in stuttering speakers, which was a novel contribution to the field. I conducted data collection, analysis, and wrote the paper.
   a. Chang SE, Kenney MK, Loucks TM, Ludlow CL. Brain activation abnormalities during speech and non-speech in stuttering speakers. Neuroimage. 2009 May 15;46(1):201-12. PubMed PMID: 19401143; PubMed Central PMCID: PMC2693291.
   b. Chang SE, Horwitz B, Ostuni J, Reynolds R, Ludlow CL. Evidence of left inferior frontal-premotor structural and functional connectivity deficits in adults who stutter. Cereb Cortex. 2011 Nov;21(11):2507-18. PubMed PMID: 21471556; PubMed Central PMCID: PMC3183422.
3. I am currently the PI of a large scale longitudinal investigation of childhood developmental stuttering. The study involves collecting multimodal neuroimaging data (DTI, resting state fMRI, and structural MRI), speech, cognitive and motor performance measures, and language development indices from each child for up to 4 time points. This is the largest, and to the best of my knowledge, the only such dataset that exists for stuttering children in the 3-10 year range. My group has published a number of novel research findings from this study, and expect to publish many more in the next few years as we continue to acquire longitudinal data points from most of our existing participants. These data will help elucidate the neurological bases of childhood stuttering, which may lead to helping find objective markers for persistent stuttering, and neural targets for intervention.
   a. Chang SE, Zhu DC. Neural network connectivity differences in children who stutter. Brain. 2013 Dec;136(Pt 12):3709-26. PubMed PMID: 24131593; PubMed Central PMCID: PMC3859219.
   b. Chang SE. Research updates in neuroimaging studies of children who stutter. Semin Speech Lang. 2014 May;35(2):67-79. PubMed PMID: 24875668.
   c. Chang SE, Zhu DC, Choo AL, Angstadt M. White matter neuroanatomical differences in young children who stutter. Brain. 2015 Mar;138(Pt 3):694-711. PubMed PMID: 25619509.
   d. Wieland EA, McAuley JD, Dilley LC, Chang SE. Evidence for a rhythm perception deficit in children who stutter. Brain Lang. 2015 May;144:26-34. PubMed PMID: 25880903.

D. RESEARCH SUPPORT

Ongoing Research Support

2014/12/01-2017/11/30
Matthew K. Smith Foundation grant
Chang, Soo-Eun (PI)
Neuroscience guided translational research in stuttering
The goals of the projects include testing novel methods in real-time neurofeedback and non-invasive brain stimulation to apply to therapeutic interventions in stuttering.
Role: PI

2014/11/21-2016/12/01
American Speech-Language Hearing Foundation Clinical Research Grant
Chang, Soo-Eun (PI)
Enhancing speech motor function in stuttering speakers with neuromodulation: A tDCS Study

The goal of this project is to test the potential of using a noninvasive brain stimulation technique to drive neuroplastic changes conducive to fluent speech motor processing.
Role: PI

2014/10/01-2016/09/30
Rauner Family Foundation Pilot Grant
Fitzgerald, Chang (PI)
Psychological and neurophysiological risk markers of persistent stuttering in early development
This project aims to establish psychological and neurophysiological predictors of persistent stuttering in early development.
Role: CPI

2010/09/29-2016/03/31
R01 DC011277-05, National Institute on Deafness and Other Communication Disorders (NIDCD)
Chang, Soo-Eun (PI)
Sexual dimorphism of neural development underlying childhood stuttering
Role: PI

2010/09/29-2016/03/31
R01 DC011277-04S1, National Institute on Deafness and Other Communication Disorders (NIDCD)
Chang, Soo-Eun (PI)
Sexual dimorphism of neural development underlying childhood stuttering
Role: PI

2014/03/01-2016/02/29
Research in Autism, Intellectual and Neurodevelopmental Disabilities Grant
McAuley, Chang, Wade (PI)
Neural mechanisms of developmental stuttering: Translation of an animal model of rhythm processing to assessment and intervention
The project aims are to foster an innovative interdisciplinary collaborative research program in stuttering to advance understanding of the neural mechanisms of developmental stuttering, which may lead to finding ways to improve diagnosis, assessment and treatment of stuttering.
Role: CPI

Completed Research Support

2013/03/14-2014/05/14
Grammy Foundation grant
McAuley, Chang, Wade (PI)
Rhythm processing deficits in developmental stuttering
The project goals are to conduct the first systematic investigation of the potential role of rhythm processing deficits in developmental stuttering.
Role: CPI

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Ratner, Nan Bernstein

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

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Tufts University, Medford, MA	B. A.	06/1974	Child Study/Linguistics
Temple University, Philadelphia, PA	M. A.	06/1976	Speech Pathology
Boston University, Boston, MA	Ed.D.	05/1982	Applied Psycholinguistics

A. Personal Statement:

My research program over the past thirty years has spanned a number of areas in both typical and atypical speech/language processing, in both children and adults. More specifically, my most common recurrent themes have addressed typical and atypical fluency across the lifespan (e.g., stuttering, use of fluency as a marker of language proficiency in other populations), and the role of the language environment in first language learning.

My most recent and ongoing collaborations involve 1) linguistic predictors of persistence and recovery from developmental stuttering (with Christine Weber, [previously publishing as Weber-Fox] at Purdue, and with Soo-Eun Chang/Ho Ming Chow at Michigan); 2) use of the NIH-supported TalkBank initiative to generate both new norms for clinical language assessment measures in children and adults (with Brian MacWhinney of CMU), as well as education of researchers and clinicians to make use of this resource; 3) potential input predictors of preschool language development (with Rochelle Newman, at UMD, and with Erika Hoff at FAU).

These first two efforts make me an appropriate co-investigator on this ECR R21 application for the following reasons:

1) I have been affiliated with the TalkBank project since its inception, and as current consultant to the project, I have collaborated on the development of fluency codes (integral to the proposed grant) and child language appraisal routines currently implemented by the KidEval utility. This grant application proposes to use KidEval output (e.g., lexical appraisal by TTR, NDW, VocD; syntactic appraisal by MLU, IPSYN and DSS) to contrast language performance of the children in the persistent, recovered and peer comparison groups, as well as inform activation profiles obtained during the story generation task.
2) I have historically led the fruitful investigation of potential linguistic deficits in both children and adults who stutter, starting with my early work in the 1980's and continuing to the present day. This work is now broadly viewed as critical to understanding stuttering, which appears to intersect with the language production system.

   Recent publications most relevant to this proposal:

   a) Bernstein Ratner, N. & Newman, R. (2009) Effects of word frequency and phonological neighborhood characteristics on confrontation naming in children who stutter and normally fluent peers. *Journal of Fluency Disorders, 34*, 225-241. PMID: 20113768
   b) Berl, M., Mayo, J., Parks, E., Rosenberger, L., Van Meter, J., Bernstein Ratner, N., Vaidya, C., & Gaillard, W.D. (2012) Regional differences in the developmental trajectory of lateralization of the language network, Human Brain Mapping, doi:10.1002/hbm.22179. PMID: 23033058
   c) Bauman, J., Hall, N., Wagovich, S., Weber-Fox, C. & Bernstein Ratner, N. (2012). Past tense marking in the spontaneous speech of preschool children who do and do not stutter. Journal of Fluency Disorders, 37(4):314-24. PMID: 23218214

B. Positions and honors

Positions:

1983-1989 The University of Maryland, College Park
Assistant Professor, Department of Hearing and Speech Sciences

1989-1992 The University of Maryland, College Park
Associate Professor, Department of Hearing and Speech Sciences

1993-1999 The University of Maryland, College Park
Associate Professor and Chairman, Department of Hearing and Speech Sciences

1999-2014 The University of Maryland, College Park
Professor and Chairman, Department of Hearing and Speech Sciences

2014- pres Professor, Department of Hearing and Speech Sciences
Participating faculty, Program in Neuroscience and Cognitive Science
Research professor, Language Sciences

Other positions:

Co-editor-in-Chief, *Seminars in Speech and Language*
Editorial Board, *Journal of Communication Disorders*
Editorial consultant (past 3 years): *Journal of Speech, Language and Hearing Research* (language and speech sections), *Journal of Child Language*, *American Journal of Speech-Language Pathology, Journal of Fluency Disorders, Child Development, JASA.*

Honors:

1991 Honors of the Maryland Speech-Language-Hearing Association
1996 Fellow, American Speech-Language-Hearing Association
2006 Distinguished Researcher Award, International Fluency Association
2012 Miegunyah Visiting Fellow, University of Melbourne
2013 Dean's Medal, University of Maryland
2015 Fellow, American Association for the Advancement of Science (AAAS) – Psychology
2015 Honors, American Speech-Language-Hearing Association

C. Contribution to Science

1. A longstanding focus of my research is in trying to better understand stuttering. As a unique childhood-onset communication disorder, it now appears clear that stuttering involves language processing difficulties as well as speech production problems. I was among the first to notice this relationship, which has now been incorporated into multi-factorial models of stuttering developed by diverse research labs worldwide.
    a. Bernstein, Nan (1981). Are there constraints on childhood dysfluency? *Journal of Fluency Disorders, 6*, 341-350. doi:10.1016/0094-730X(81)90021-8
    b. Bernstein Ratner, Nan & Catherine C. Sih (1987). The effects of gradual increases in sentence length and complexity on children's dysfluency. *Journal of Speech and Hearing Disorders, 52* (3), 278-287. PMID: 3455450
    c. Newman, R. & Bernstein Ratner, N. (2007). The role of selected lexical factors on confrontation naming accuracy, speed and fluency in adults who do and do not stutter. *Journal of Speech, Language and Hearing Research, 50*, 196-213. PMID: 17344559
    d. Wagovich, S. & Bernstein Ratner , N. (2007). Frequency of verb use in young children who stutter. Journal of Fluency Disorders, 32, 79-94. PMID: 17499123
    e. Bernstein Ratner, N., Newman, R., & Strekas, A. (2009). Effects of word frequency and phonological neighborhood characteristics on confrontation naming in children who stutter and normally fluent peers. *J. of Fluency Disorders, 34*, 225-241. PMID: 20113768

2. A natural outgrowth of this program of research has been the realization that speech fluency serves as a marker of language formulation difficulty in other populations. This discovery may enable language-free indicators of language disorder, as well as inform impairment in both first and subsequent language acquisition by both children and adults with most of my recent work in stuttering, this work has relied extensively in approach on using TalkBank utilities to augment experimental work with computer-assisted language sample analysis.

a. Steinberg ME, Ratner NB, Gaillard W, Berl M. (2013) Fluency patterns in narratives from children with localization related epilepsy. *Journal of Fluency Disorders, 38*, 193-205. PMID: 23773671
b. Bernstein Ratner, Nan (2013). Fluency in late talkers. In L. Rescorla & P. Dale (eds.) *Late talkers: from theory to practice*. Baltimore: Brookes (pp 129-144).
c. Boscolo B, Ratner NB, Rescorla L. (2002) Fluency characteristics of children with a history of Specific Expressive Language Impairment (SLI-E). *American Journal of Speech-Language Pathology, 11,* 41-49. PMID: 26225412

3. Much of my other research focuses on parental contributions to children's language development and other precursors of preschool language skill. Can we identify earlier indicators of children's success in learning language? Are children's caretakers important influences on their language development – if so, how can we use this knowledge to improve children's communicative outcomes?
    a. Newman, R. S., Bernstein Ratner, N., Jusczyk, A. M., Jusczyk, P. W. & Dow, K. A. (2006). Infants' early ability to segment the conversational speech signal predicts later language development: A retrospective analysis. *Developmental Psychology, 42*(4), 643-655. PMID: 16802897
    b. Torrington Eaton C. & Bernstein Ratner N. (2013) Rate and phonological variation in preschool children: effects of modeling and directed influence. *J Speech Lang Hear Research*, 56(6):1751-63. PMID: 23882009
    c. Miles S., & Bernstein Ratner N. (2001) Parental language input to children at stuttering onset. J *Speech Lang Hear Research.* 44(5):1116-30. PMID: 11708531
    d. Newman, R. S., Rowe, M. & Bernstein Ratner, N. (2015) The role of child-directed-speech and infant processing skills in language development. *Journal of Child Language,*1-16. PMID: 26300377

4. A more recent focus of my research is the investigation of progressive language impairment in childhood temporal lobe epilepsy (TLE), which has been carried out in conjunction with Madison Berl and William Gaillard at CNMC. We have discovered progressive attrition of language skills in children with TLE not currently monitored by most academic and medical protocols. Relevant to this proposal, I have helped the team to integrate behavioral (language use) manifestations of the disorder with brain imaging results to achieve a more nuanced view of how atypical anatomy/physiology relates to functional use of language in children.
    a. Strekas, A., Bernstein Ratner N., Berl, M., & Gaillard WD. (2013) Narrative abilities of children with epilepsy. *Int J Lang Commun Disorders*; 48(2):207-19. PMID: 23472960
    b. Berl, M., Mayo, J., Parks, EN, Rosenberger, LR, VanMeter, J, Bernstein Ratner, N., Vaidya, CJ, & Gaillard, WD. (2014) Regional differences in the developmental trajectory of lateralization of the language network. Hum Brain Mapping, 35(1):270-84. PMID: 23033058
    c. Berl MM, Duke ES, Mayo J, Rosenberger LR, Moore EN, VanMeter J, Ratner NB, Vaidya CJ, Gaillard WD. (2010) Functional anatomy of listening and reading comprehension during development. Brain & Language,114(2):115-25. PMID: 20656105

5. I have also investigated the strengths and pitfalls of translating research findings to evidence-based practice in speech-language pathology:
    a. Nail-Chiwetalu, B. & Bernstein Ratner N. (2007) An assessment of the information-seeking abilities and needs of practicing speech-language pathologists. J Med Libr Assoc, 95(2):182-8. PMID: 17443251
    b. Bernstein Ratner N. (2006) Evidence-based practice: an examination of its ramifications for the practice of speech-language pathology. *Lang Speech Hear Serv Sch*. 37(4):257-67. PMID: 17041074
    c. Bernstein Ratner, N. (2005) Evidence-based practice in stuttering: Some questions to consider. J Fluency Disorders, 30(3):163-88. PMID: 15961152

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1-UVaaDdREZ/bibliography/40436718/public/?sort=date&direction=ascending

D. Research Support

Ongoing research support

9R01HD082736-11 (2014-2019); PI: Brian MacWhinney. Role: Consultant.
"Computational Analysis of Child Language Transcript Data"
This grant exploits the richness of the TalkBank/Childes archive to re-norm basic clinical measures of child language ability (such as MLU, TTR, etc.) and offers outreach to expand archive/CLAN use by clinicians.

NIDCD: 1 R01 HD068421-01 (2011-16; Erika Hoff, PI; Role: Consultant).
"*Early Dual Language Development in Children from Spanish-Speaking Families".*
This grant investigates the pace of bilingual language acquisition in toddlers, with special emphasis on the role of parental input in each household language.

University of Maryland BSOS Dean's Research Initiative, Collaboratory Grant (Role: Co-PI) 2014/2015
"Language as a means of assessing children's concussion"
This internally-funded research grant includes series of studies investigating the effect of sports-related concussion on children's language skills, and supports developing a device to help assess concussion in young children. It includes a collaboration between 6 faculty members, 3 of whom (Colin Phillips, Nan Bernstein Ratner, and Rochelle Newman) serve as core faculty on the current proposal.

Completed Research Support (last 3 years)
NSF BCS 074512 (2008-2013) Role: Co-I
"Speech and nonspeech predictors of later language development" (PI: Rochelle Newman)
This project explores the potential contributing roles of speech segmentation, statistical learning, and maternal input in children's later language acquisition by examining skills concurrently in the same child cohort.

NSF IGERT (2008-2013) Role: Participating Faculty
"Biological and computational foundations of language diversity" This IGERT project supports interdisciplinary doctoral training and research in the foundations of language diversity.

NSF ADVANCE Program for Inclusive Excellence Dougherty (Role: Co-PI) 5/12-5/13
"Maternal depression and child language development"
This internally-funded project with a junior faculty member in Psychology investigated the potential role of depressed, previously depressed and typical mothers' speech and language behaviors on the expressive language outcomes of their children.

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PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix:
First Name*: Ho Ming
Middle Name:
Last Name*: Chow
Suffix:

2. Human Subjects

Clinical Trial? ○ No ● Yes
Agency-Defined Phase III Clinical Trial?* ● No ○ Yes

3. Permission Statement*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

● Yes ○ No

4. Program Income*

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)*

Funding Opportunity Number: PAR-16-057. Received Date: 2016-02-23T15:48:23.000-05:00

PHS 398 Cover Page Supplement

5. Human Embryonic Stem Cells

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

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, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: ○ Yes ● No

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

Previously Reported*: ○ Yes ○ No

7. Change of Investigator / Change of Institution Questions

❑ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

❑ Change of Grantee Institution

Name of former institution*:

PHS 398 Modular Budget

OMB Number: 0925-0001
Expiration Date: 10/31/2018

Budget Period: 1

Start Date: 09/01/2016 End Date: 08/31/2017

A. Direct Costs

	Funds Requested ($)
Direct Cost less Consortium Indirect (F&A)*	[redacted]
Consortium Indirect (F&A)	[redacted]
Total Direct Costs*	[redacted]

B. Indirect (F&A) Costs

	Indirect (F&A) Type	Indirect (F&A) Rate (%)	Indirect (F&A) Base ($)	Funds Requested ($)
1.	[redacted]	[redacted]	[redacted]	[redacted]
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): Department of Health and Human Services, Jackie Garner, 312-886-6432

Indirect (F&A) Rate Agreement Date: 05/10/2013

Total Indirect (F&A) Costs: [redacted]

C. Total Direct and Indirect (F&A) Costs (A + B)

Funds Requested ($): [redacted]

Funding Opportunity Number: PAR-16-057. Received Date: 2016-02-23T15:48:23.000-05:00

PHS 398 Modular Budget

Budget Period: 2
Start Date: 09/01/2017 End Date: 08/31/2018

A. Direct Costs

	Funds Requested ($)
Direct Cost less Consortium Indirect (F&A)*	[redacted]
Consortium Indirect (F&A)	[redacted]
Total Direct Costs*	[redacted]

B. Indirect (F&A) Costs

	Indirect (F&A) Type	Indirect (F&A) Rate (%)	Indirect (F&A) Base ($)	Funds Requested ($)
1.	MTDC	[redacted]	[redacted]	[redacted]
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): Department of Health and Human Services, Jackie Garner, 312-886-6432

Indirect (F&A) Rate Agreement Date: 05/10/2013

Total Indirect (F&A) Costs: [redacted]

C. Total Direct and Indirect (F&A) Costs (A + B)

Funds Requested ($): [redacted]

Funding Opportunity Number: PAR-16-057. Received Date: 2016-02-23T15:48:23.000-05:00

PHS 398 Modular Budget

Budget Period: 3
Start Date: 09/01/2018 End Date: 08/31/2019

A. Direct Costs

	Funds Requested ($)
Direct Cost less Consortium Indirect (F&A)*	[redacted]
Consortium Indirect (F&A)	[redacted]
Total Direct Costs*	[redacted]

B. Indirect (F&A) Costs

	Indirect (F&A) Type	Indirect (F&A) Rate (%)	Indirect (F&A) Base ($)	Funds Requested ($)
1.	MTDC	[redacted]	[redacted]	[redacted]
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): Department of Health and Human Services, Jackie Garner, 312-886-6432

Indirect (F&A) Rate Agreement Date: 05/10/2013

Total Indirect (F&A) Costs: [redacted]

C. Total Direct and Indirect (F&A) Costs (A + B)

Funds Requested ($): [redacted]

Funding Opportunity Number: PAR-16-057. Received Date: 2016-02-23T15:48:23.000-05:00

PHS 398 Modular Budget

Cumulative Budget Information

1. Total Costs, Entire Project Period

Section A, Total Direct Cost less Consortium Indirect (F&A) for Entire Project Period ($)	[redacted]
Section A, Total Consortium Indirect (F&A) for Entire Project Period ($)	[redacted]
Section A, Total Direct Costs for Entire Project Period ($)	[redacted]
Section B, Total Indirect (F&A) Costs for Entire Project Period ($)	[redacted]
Section C, Total Direct and Indirect (F&A) Costs (A+B) for Entire Project Period ($)	[redacted]

2. Budget Justifications

Personnel Justification	[redacted]ModularJustification.pdf
Consortium Justification	UofMaryland_Justification.pdf
Additional Narrative Justification	

Funding Opportunity Number: PAR-16-057. Received Date: 2016-02-23T15:48:23.000-05:00

Budget Justification

[redacted]

Senior/key personnel:

Ho Ming Chow, Ph.D., PD/PI (4.8 calendar months) will be responsible for overseeing the overall direction and implementation of this project to achieve the proposed specific aims. Dr. Chow is experienced in managing fMRI studies in adults who stutter and is an expert fMRI de-noising techniques and analyses.

Soo-Eun Chang, Ph.D., Co-I (0.6 calendar month) will provide her expertise in pediatric neuroimaging and work in collaboration with the PI on the interpretation of imaging results. Dr. Chang has extensive experience in using multimodal neuroimaging techniques to study functional and structural anomalies in children who stutter. She is also a certified Speech-Language Pathologist who can supervise all behavioral and fluency assessment procedures that take place prior to MRI participation.

Other Personnel:

Emily O'Dell Garnett, Ph.D. (2.4 calendar months) is a certified Speech-Language Pathologist and experienced in stuttering research. Dr. Garnett will carry out behavioral and speech assessments and assist in subject recruitment and MRI data collection.

Budget Justification for University of Maryland

Personnel

Nan Bernstein Ratner, Ph.D., Co-I (.45 academic months) is a widely published expert in stuttering research and will be responsible for the execution of fluency analyses and generation of clinical language assessment measures using the NIH-supported TalkBank initiative in this project. She will also assist the PI in the interpretation of participants' linguistic profiles in related to recovery and persistence of stuttering.

Research Assistant, TBA, (2.9 CM) An undergrad or master's level research assistant will work hourly under supervision of Co-I Ratner in assisting with fluency analyses and generation of clinical language assessment measures using the NIH-supported TalkBank initiative in this project.

Fringe Benefits

The University of Maryland does not have a fringe benefit rate. Contract/grant accounts will be charged for the actual fringe benefit amount used. Fringe benefits have been calculated for Dr. Ratner at a rate of [redacted] Included: pension plan contributions; social security; Medicare taxes; unemployment compensation insurance; subsidies for health, life, and disability insurance; vacation; and sick leave.

Indirect Costs

Indirect costs are computed at a rate of [redacted] applied to all costs.

Indirect Costs

Indirect costs are computed at a rate of [redacted] applied to all costs.

Year 1: Estimated Total Costs [redacted]

Year 2: Estimated Total Costs [redacted]

Year 3: Estimated Total Costs [redacted]

PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

1. Introduction to Application (for RESUBMISSION or REVISION only)	
2. Specific Aims	SpecificAims.pdf
3. Research Strategy*	ResearchStrategy.pdf
4. Progress Report Publication List	
Human Subjects Sections	
5. Protection of Human Subjects	ProtectionOfHumanSubjects.pdf
6. Inclusion of Women and Minorities	InclusionOfWomanAndMinorities.pdf
7. Inclusion of Children	InclusionOfChildren.pdf
Other Research Plan Sections	
8. Vertebrate Animals	
9. Select Agent Research	
10. Multiple PD/PI Leadership Plan	
11. Consortium/Contractual Arrangements	
12. Letters of Support	LetterOfSupport_Combined.pdf
13. Resource Sharing Plan(s)	ResourseSharingPlan.pdf
Appendix (if applicable)	
14. Appendix	

Tracking Number: GRANT12102741

Funding Opportunity Number: PAR-16-057. Received Date: 2016-02-23T15:48:23.000-05:00

SPECIFIC AIMS

Developmental stuttering is a speech disorder with a prevalence of 1% and a lifetime-incidence of approximately 5% in the U.S.A. Stuttering can have a strong negative impact on the individual's social, emotional, academic, and vocational development. Interestingly, about 80% of children who stutter (CWS) recover naturally within a few years of stuttering onset [1, 2]. The high rate of recovery during childhood signifies that neuroplasticity in children play a critical role in overcoming whatever deficits that underlie stuttering. The current challenge is to understand the deficits that disrupt fluent speech production and the neural processes associated with recovery from stuttering in CWS. Without such understanding, we are hindered in our ability to develop more effective therapeutic interventions for childhood stuttering.

Finding from recent neuroimaging studies of CWS, employing non-discourse, relatively simple speaking tasks (e.g., single-word production) or non-speaking contexts (e.g., wakeful rest), indicate that stuttering is associated with functional and structural anomalies in (sub)cortical areas classically associated with speech-motor control [3, 4]. However, these procedures are limiting because stuttering typically do not occur during simple speaking tasks. Thus, they do not optimally inform the neurophysiology of childhood stuttering. The most ecologically-valid context to study stuttering is continuous speech production, because in this context, symptoms of stuttering are most apparent. A major obstacle to studying children's continuous speech is that speech-related movements severely contaminate data collected from non-invasive neuroimaging methods such as functional magnetic resonance imaging (fMRI). To overcome this obstacle, the current application proposes a novel methodology [5] by which fMRI can be used to empirically study children's neural processes associated with fluent and stuttered speech occurring during continuous speech production to help identify the neurological deficits underlying stuttering and how the disorder resolves itself.

Our *long-term goal* is to develop effective therapeutic interventions to treat and prevent persistent stuttering during childhood. In pursuit of that goal, the immediate *objective* of the present application, which is the next step in pursuing that goal, is to determine brain activity patterns associated with continuous speech production in children with persistent (pCWS) and recovered from stuttering (rCWS). The *central hypothesis* is that persistent stuttering is associated with anomalous brain activity in the neural circuits for speech-motor control in the left hemisphere, while recovery from stuttering is associated with greater involvement of right frontal areas. The *rationale* of this proposed research is that an empirically-based understanding of brain activity patterns associated with continuous speech production of pCWS and rCWS is foundational for the development of therapeutic interventions attempting to modify anomalous activity. The proposed work tests our central hypothesis and accomplishes our objective with the following aims:

Specific Aim 1: Identify brain activity associated with continuous speech production that characterizes persistent stuttering. In this aim, we examine brain activity associated with fluent (**sub-aim 1a**) and stuttered speech (**sub-aim 1b**) in children with persistent stuttering (pCWS). Based on our preliminary data, we hypothesize that **H1a**: The analysis of fluent speech production of pCWS, compared to that of children who do not stutter (CWNS), will reveal anomalous brain activity associated with persistent stuttering in the cortical areas supporting speech monitoring, including the posterior temporal gyrus and the inferior frontal gyrus in the left hemisphere. **H1b**: Instances of stuttering in pCWS, in contrast to their fluent speech will reveal anomalous brain activity associated with stuttering behaviors in the areas supporting motor planning and control, including the supplementary motor area, the premotor cortex and the basal ganglia.

Specific Aim 2: Identify brain activity associated with continuous speech production that characterizes recovery from stuttering. Based on preliminary data, we hypothesize that **H2a**: children who are recovered from stuttering (rCWS) will exhibit less anomalous activity than pCWS in the left perisylvian areas and **H2b**: rCWS, in comparison to CWNS, will exhibit increased activity in the right frontal areas.

Findings of the proposed projects are expected to i) identify patterns of brain activity associated with persistent stuttering during continuous speech (the context in which stuttering is most likely to occur), ii) advance our understanding of children's speech production and how these processes are disturbed, resulting in overt instances of stuttering (e.g., sound/syllable repetitions, prolongations, and blocks) and iii) provide insights into the neural processes of continuous speech after recovery from stuttering. Such outcomes will have a *positive translational impact* on future development of better treatment strategies for childhood stuttering. Moreover, applying a validated fMRI methodology that studies neural processes of continuous speech production provides the groundwork for future investigations using advanced data analysis approaches (e.g., functional connectivity), new fMRI technologies (e.g. multiband acquisition) and longitudinal experimental designs to study speech disorders.

A. SIGNIFICANCE

Burden of childhood stuttering: While most speakers take fluent speech for granted, approximately 3 million children and adults in the U.S.A with developmental stuttering struggle to speak fluently every day. Such struggle results in lower quality of life for people who stutter [6]. To develop better treatment strategies and minimize the potentially adverse impacts of stuttering on children's academic, social, and future vocational accomplishments and development [7], there is a need to better understand the neurophysiology underlying childhood developmental stuttering and the neural processes associated with its persistence and recovery.

A gap in the *current understanding of neurophysiology associated with childhood stuttering*: Neuroimaging studies of people who stutter have contributed important insights into the neural processes associated with both speech production and stuttering [8-10]. To date, however, these studies have mainly focused on adults, and neuroimaging studies examining speech production in children who stutter (CWS) remain scarce. The absence of neuroimaging studies on CWS's speech processes is largely due to technological constraints in imaging children's brains during continuous speech production.

Advancing our understanding of neural processes of continuous speech production: A recent advancement in fMRI de-noising techniques now permits the use of fMRI to study continuous speech [5]. This technique - developed by the present application's PI (Chow) - uses spatial Independent Component Analysis (sICA), a signal un-mixing algorithm to separate speech and movement artifacts from signals originating from neuronal activity. By using fMRI with this sICA de-noising technique, it is possible to empirically study the anomalous brain activity associated with pCWS's continuous speech production as well as pCWS's compensatory adaptations to these brain anomalies. It also allows acquisition of data from the whole brain including subcortical areas important for speech-motor control.

Impact on future development of better interventions: Identification of activity patterns associated with persistence and recovery of childhood stuttering would potentially guide future development of therapeutic interventions by providing targets for brain simulation techniques such as transcranial direct current simulation and other neuromodulation techniques to augment brain regions related to recovery and fluent speech.

Scientific premises: The proposed study assumes that fMRI measurements (i.e., BOLD) is a good estimation of brain activity. BOLD, an indirect measure of neuronal activity, arises from local changes in capillary blood oxygenation level triggered by nearby neuronal firing. Although this neurovascular coupling is not fully understood, tight correspondence between BOLD and neuronal activity has been demonstrated using simultaneous recordings of fMRI and neurophysiological measures in animals [11, 12] and humans [13]. Another premise is the validity of the proposed de-noising method. It will be addressed comprehensively in the Approach section.

B. INNOVATION

Imaging methodologies: To date, using fMRI to capture brain responses associated with longer speech utterances has been severely limited because speech-related artifacts considerably contaminate fMRI images [14]. The only brain imaging technologies appropriate to study neural correlates of continuous speech production were positron emission tomography (PET) and functional near-infrared spectroscopy (fNIRS). However, PET is not justified with children because of radioactive exposure. FNIRS, on the other hand, cannot detect activity in deep brain structures including the basal ganglia, a subcortical structure seemingly essential for fluent speech production [15] which has been linked to stuttering behaviors [16]. Thus, neither PET nor fNIRS are optimal for studying CWS's continuous speech production. In contrast, our approach removes speech-related noise from fMRI by using sICA to decompose fMRI signals into a set of statistically independent components, each consisting of a spatial map and a time course. Because brain activity and speech-related noise are associated with distinct spatial patterns (Fig. 1), they will be decomposed into separate components by sICA. Our previous research shows that noise spatial patterns can be identified effectively by using six noise templates and three measures of components' signal intensity: i) out-of-the-brain ratio, ii) scattering degree (detection of checkerboard patterns) and iii) slice-wise variation (detection of interleaved patterns) [5]. Noise components can then be removed from functional images. Thus, the proposed research is innovative because the *sICA fMRI de-noising technique will, for the first time, enable the study of continuous speech production in children with high spatial resolution*. Moreover, the sICA fMRI procedure can examine the activity of cortical and subcortical areas during children's continuous speech production, data previously unattainable using methodologies such as fNIRS. Furthermore, since fMRI provides relatively high temporal resolution compared to PET, we can potentially distinguish brain activity associated with stuttering instances from that associated with fluent

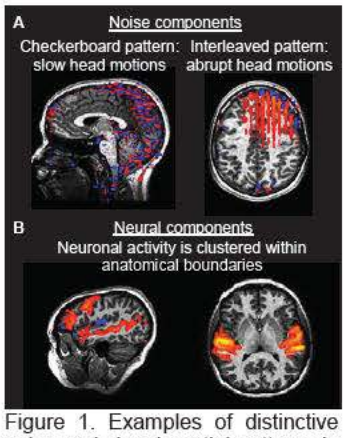

Figure 1. Examples of distinctive noise and signal spatial patterns in sICA components (ICs) of an adult participant. Top row (A) shows ICs associated with slow (left) and abrupt head movements (right). Bottom Row (B) shows ICs associated with neuronal activity. Images adopted from [5]

speech, providing insights into how stuttering instances emerge from continuous speech.

Neural characteristics of persistence and recovery: The proposed project exploits an existing participant pool from a longitudinal neuroimaging study of CWS headed by Co-I Dr. Chang. Since 2010, Dr. Chang's team has monitored neural, cognitive, and speech development of over 60 CWS and 60 fluent peers. This longitudinal participant tracking allows objective identification of pCWS and rCWS. Thus, the present proposal is uniquely positioned to empirically study brain activity associated with stuttering persistence and recovery.

C. APPROACH

C1. FEASIBILITY. The validation and technical details of the proposed sICA fMRI de-noising method have been published in [5]. Moreover, PI's previous work has demonstrated we can obtain meaningful information about the neural processes of continuous speech production using fMRI [17, 18]. Three preliminary feasibility studies of the proposed method important to the current application are reported immediately below.

C1.1. Preliminary Study 1: Feasibility of removing image artifacts associated with abrupt head movements. Because severe movement artifacts may occur during children's continuous speech production, removing these artifacts is critical to the proposed project. In fact, even during resting-state scans, young participants often make large, abrupt head movements. Such artifacts are known to drastically increase volume-to-volume variation of BOLD signals, i.e., DVARS [14, 19]. Thus, we employed extant resting-state data to evaluate the effectiveness of our sICA de-noising technique in removing movement artifacts. The association between head movements and DVARS, measured by framewise displacement (FD) before sICA de-noising is illustrated in Fig. 2A and Fig. 2B (red line), generated from a 7-year-old participant during a resting-state fMRI scan. After sICA de-noising, movement-induced DVARS diminished markedly (Fig. 2B, green line). To show that these findings are not isolated to this participant, we calculated DVARS *before* (i.e., uncorrected) and *after* de-noising of all 45,000+ volumes of our 281 resting-state fMRI scans collected from 50 CWS and 45 CWNS (aged 3-13 years). The red bars in Fig. 2C show that, as expected, DVARS before sICA de-noising (uncorrected) increased with head movement magnitude (r=0.55, p<0.001). Similar results has been published in [5] using a third-party pediatric fMRI data set. In contrast, after sICA de-noising, DVARS remained at a similar level (<1%) for head movements less than 9 mm (Fig. 2C, green bars). These findings strongly indicate that our technique can remove fMRI artifacts related to abrupt head movements in children. In PI's previous fMRI study of continuous speech production (see C2.2 for details), abrupt head movements > 9 mm were very rare in adults who stutter (AWS), occurring only in less than 0.15% of the total fMRI volumes obtained from 29 AWS. We expect that abrupt head movements occur more frequent in CWS but most of them will still be within the workable range of our de-noising technique.

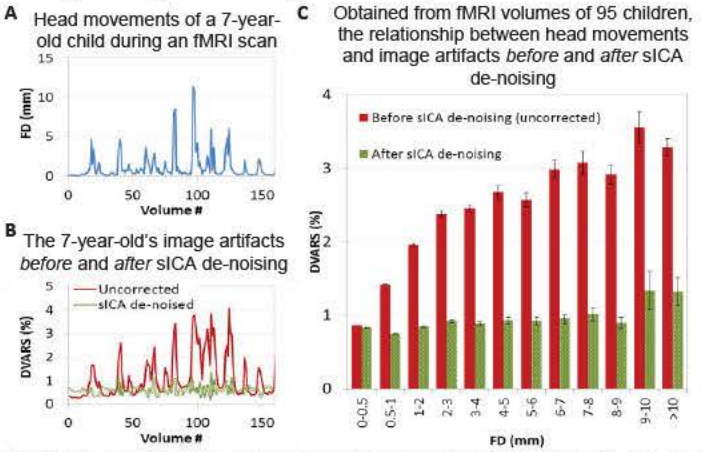

Figure 2. Relationship between framewise displacement (FD), i.e., an empirical sum of motion between consecutive volumes in all 6 motion directions and volume-to-volume variation of fMRI signals (DVARS) before and after sICA de-noising. Panel A shows FD of a 7-year-old participant during a 6-minute resting-state scan. Panel B shows that DVARS (red line) of that participant is strongly associated with FD. After sICA de-noising (Panel B, green line), movement-induced DVARS reduced to the normal range. Panel C shows the means and standard errors of DVARS *before* (uncorrected) and *after* sICA de-noising at different levels of head movements, based on 45,000+ fMRI volumes from 50 CWS and 45 CWNS. DVARS of the uncorrected volumes increased with FD (red bars) but this relationship greatly diminished after sICA de-noising (green bars).

C1.2. Preliminary Study 2: Feasibility of detecting brain activity associated with continuous speech production using fMRI. Another critical issue is to determine whether our sICA de-noising technique can remove noise, without also unintentionally discarding a substantial proportion of signals originating from neuronal activity. Thus, we compared fMRI with our technique to PET [5]. PET is considered the gold standard for imaging speech production because it is less susceptible to movement artifacts. Fig. 3 shows that the activity pattern associated with a storytelling task vs. over-learned speech in 18 healthy adults obtained from fMRI with sICA de-noising was highly similar to that obtained from PET. This confirms that signals originated from neuronal activity are preserved after sICA de-noising. Moreover, statistical power is considerably higher for de-noised fMRI than PET.

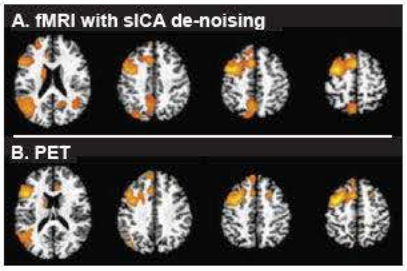

Figure 3. Brain activity pattern associated with a continuous speech production task measured by fMRI with the proposed sICA de-noising technique (A) and PET (B) (n = 18 adults). Both imaging methods generated highly similar results, indicating that brain activity associated with continuous speech production can be studied using fMRI. Images adopted from [17].

C1.3. Preliminary Study 3; Feasibility of using fMRI to image children's brain activity during continuous speech production. In this preliminary study, a typically-developing, 8-year-old child successfully com-

pleted the fMRI study of speech production proposed in the current application (see C3.4 for details), with moderate head movements (FD = 0-2.5 mm). Results of this child's storytelling compared with overlearned speech (e.g., "A B C ...") were similar to those from previous adult studies [10, 17] (also see Fig. 3), that is, there was increased activity in the perisylvian regions (Fig. 4). Thus, results of this preliminary study indicate that it is feasible to obtain usable fMRI data from children's continuous speech production.

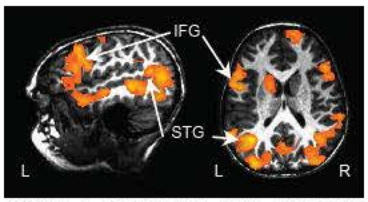

Figure 4. Compared with automatic speech, storytelling elicited increased brain activity (indicated in orange) in the perisylvian regions of an 8-year-old participant (p<0.01, corrected)

C2. JUSTIFICATION. Theoretical (C2.1) and empirical (C2.2 & C2.3) supports of the hypotheses related our Specific Aims are presented immediately below.

C2.1. Neuroanatomical model of stuttering. Early imaging studies using PET to examine neural activity associated with continuous speech production in adults who stutter (AWS) reported anomalous brain activity in the ventral premotor cortex (vPMC), the supplementary motor area (SMA), the basal ganglia (BG), the cerebellum, the inferior frontal gyrus (IFG), and the superior temporal gyrus (STG) [8, 9]. Theoretical accounts suggest that these regions form the neural circuits for speech-motor control and that disruptions to these circuits lead to stuttering behaviors [20]. A simplified neuroanatomical model of stuttering based on the models proposed by Guenther and colleagues [21, 22] posits that stuttering is a result of deficits in monitoring and converting sound- to motor-based representations of speech via the interactions among left STG and IFG/vPMC (Fig. 5, Path 1). This deficit is believed to be partially compensated for by the involvement of right IFG/vPMC, leading to fluent speech produced by stuttering speakers [20] (Fig. 5, Path 2). When this compensatory process fails, execution of articulatory movements subserved by (sub)cortical motor areas including SMA, BG, and motor cortex (MC) will be affected, resulting in stuttering instances and incorrect feedback sent to left STG for speech monitoring (Fig. 5, Path 3). Although right IFG/vPMC is thought to be related to an imperfect compensatory process in AWS, we hypothesize that it may play a key role in recovery in CWS by forming an alternative pathway (Fig. 5, Path 4) to bypass deficits in left frontotemporal pathway (Fig. 5, Path 1). Recovery may also result from normalization of deficits in this pathway.

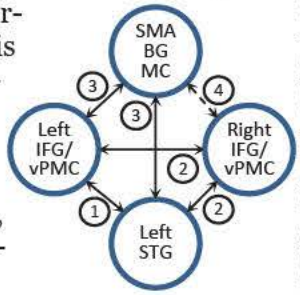

Figure 5. Based on a simplified version of Guenther and colleagues' model of stuttering [21, 22], the core deficit of stuttering is posited to be related to the interactions between speech and motor areas (*Path 1*). Sometimes, this deficit can be compensated for by the right IFG/ vPMC (*Path 2*). When this compensatory process fails, the execution of articulatory movements is affected, leading to stuttering behaviors (*Path 3*). The current proposal's PI suggests that recovery of stuttering may be related to normalization of Path 1 or the use of an alternative path in the right hemisphere (*Path 4*).

C2.2. Preliminary Study 4: Empirical support for the hypotheses of Specific Aim 1 - Identify brain activity associated with continuous speech production that characterizes <u>persistent</u> stuttering. Specific Aim 1 involves the investigation of brain activity in CWS using two approaches (sub-aim 1a and 1b). The objective of Specific Aim 1a is to identify differences in brain activity exhibited by pCWS vs. CWNS during fluent continuous speech production. According to the theoretical model presented in C2.1, we hypothesize that **H1a**: pCWS, when compared to CWNS, will exhibit anomalous activity in left perisylvian areas, including left IFG and posterior STG. The objective of Specific Aim 1b is to identify differences in brain activity exhibited by pCWS during instances of stuttered vs. fluent continuous speech production. Based on the theoretical model, we hypothesize that **H1b**: stuttered vs. fluent speech in pCWS will elicit anomalous brain activity in cortical and subcortical networks supporting motor planning and control, including SMA, vPMC and BG. *<u>Preliminary Study 4</u>*: This investigation involved the empirical study of brain activity associated with continuous speech production in 29 AWS and matched controls using the same fMRI de-noising method and analysis approaches proposed in the current application. Although results obtained from adults may not be fully applicable to children as mentioned previously, Preliminary Study 4 may be the closest approximation presently available given the lack of extant brain imaging data on children's continuous speech production. In Preliminary Study 4, participants told stories or recited nursery rhymes in 40-second trials. Each participant's speech was modelled as a sustained effect using a block regressor while stuttering instances were modeled as a transient effect using an event regressor (i.e., a mixed block/event-related design [23]) in the framework of the general linear model (GLM). Fig. 6 shows that AWS, when compared to controls, exhibited decreased activity in left perisylvian areas including left IFG and STG during fluent segments of storytelling. This attenuation of activity in AWS compared to controls has been found consistently in studies using various speaking paradigms [24-26]. Regarding H1b, AWS at stuttering instances, when com-

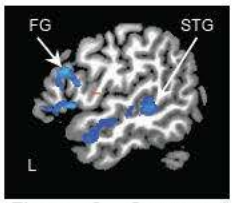

Figure 6. Compared with controls (n=26), adults who stuttering (n=29) elicited attenuated activity (indicated in blue) in the perisylvian areas during storytelling (p<0.01, corrected)

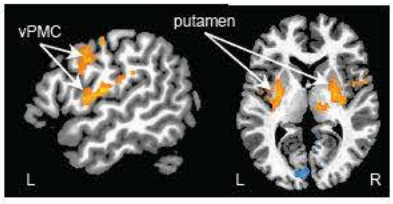

Figure 7. Comparing activity associated fluent speech production and that with stuttering instances in adults who stutter, we observed increased activity in vPMC and the putamen (indicated in orange, p<0.05, corrected)

pared to fluent speech production, exhibited increased activity in the putamen, SMA and vPMC. These results are consistent with previous reports of significant correlations between stuttering frequency and activity in the basal ganglia [8, 27, 28]. In conclusion, results of Preliminary Study 4 provide strong support of our working hypotheses for Specific Aim 1a and 1b. *Remarks on Specific Aim 1b*: Although we do not know the effect of scanner noise on CWS's stuttering frequency, both Preliminary Study 4 and a previous study suggest that AWS's stuttering frequency may be reduced by 25% in association with scanner noise [29]. Taking this into consideration, we estimate that most of our pediatric participants would stutter 10-15 times while performing the proposed speaking tasks in the scanner. While the number of in-scanner stuttering instances may seem low, in event-related fMRI studies of error processing in children, it has been demonstrated that 10-15 instances can provide sufficient power to detect the effect of interest [30-32].

C2.3. Preliminary Study 5: Empirical support for the hypotheses of Specific Aim 2 - Identify brain activity associated with continuous speech production that characterizes recovery from stuttering. The objective of Specific Aim 2 is to identify differences in brain activity exhibited by rCWS vs. CWNS and pCWS during continuous speech production. Based on the theoretical model presented in C2.1, we hypothesize that **H2a**: recovery from stuttering related to the normalization of deficits in the left frontotemporal regions and **H2b**: increased involvement of the right frontal areas. There is no direct evidence to support H2a and H2b because functional imaging studies on recovery from childhood stuttering do not exist. Since functional and structural changes usually co-occur, our working hypothesis is primarily based on our *Preliminary Study 5*, in which white-matter structural anomalies associated with rCWS and pCWS were examined. Based on 18 rCWS, 14 pCWS and 26 CWNS, results of Preliminary Study 5 (Fig. 8) shows that rCWS did not exhibit white-matter structural anomalies in left IFG that were associated with persistent stuttering. This finding suggests that, for rCWS, anomalies in the left IFG had normalized or did not exist at all in the past. In contrast, rCWS exhibited an increase in white-matter structural coherence in right IFG. This confirmed our earlier observation with a smaller sample size [33]. These structural changes in right IFG may reflect increased functional involvements underlying recovery of stuttering. Although increased activity in right IFG may reflect an imperfect compensatory mechanism in AWS [34, 35], our and others' studies of CWS suggest that it may be an important element in recovery for CWS during the critical period of brain plasticity.

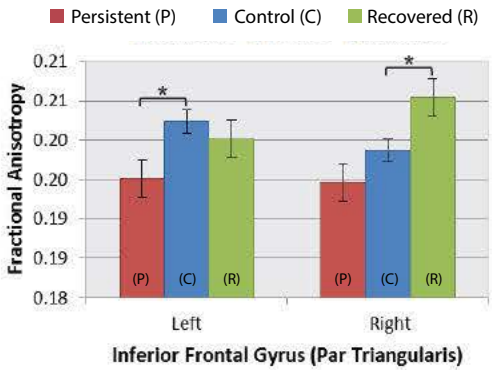

Figure 8. Fractional anisotropy (FA), a measure of white-matter structural coherence based on diffusion tensor imaging, of left and right IFG in children between 5-11 years of age, including those who recovered from stuttering (rCWS, n=14), with persistent stuttering (pCWS, n=18) and controls (CWNS, n=26). Finding indicated that relative to CWNS, rCWS did not exh bit a significant reduction of FA in left IFG, as it was in pCWS. Instead, rCWS exhibited a significant increase of FA in right IFG. Bars represent standard error and asterisks indicate a significant difference between groups (two sample *t*-test, $p<0.05$).

C3. EXPERIMENTAL DESIGN AND METHODS

C3.1 Participants. Twenty pCWS, 20 rCWS, and 20 CWNS (ages 5 to 11) will be recruited from the participant pool of co-I Dr. Chang's longitudinal neuroimaging study of childhood stuttering. To date, Chang's study has recruited more than 60 CWS and 60 normally fluent peers from areas around [redacted] All proposed participants will be monolingual English speakers without any diagnosed psychiatric or developmental disorders, other than stuttering. Since persistence or recovery from stuttering is best judged at least 2 years after onset (around 2 to 5 years of age), children who are identified as recovered or persistent are generally 5 years or older. Thus, the present proposal will involve participants from 5 to 11 years old. *Diagnosis:* According to the 4 yearly speech assessments per child obtained from Chang's study, diagnoses of recovered and persistent were determined retrospectively using these criteria: *recovered* if a child's stuttering severity score on the Stuttering Severity Instrument Edition 4 (SSI-4, [36]) decreased from 10 at intake assessment (year 1) to <10 in later assessments (year 3 or 4) and *persistent* if his or her SSI scores in years 3 and 4 exceeded 10. Diagnoses of recovered and persistent were also supported by clinician and parental reports. Inclusion criteria for CWNS included: never diagnosed as stuttering, no family history of stuttering, lack of parental concern for their child's fluency and the child's SSI score was <6. Using these criteria, we have identified 17 rCWS and 28 pCWS with certainty. By June 2016, we expect to have 25 rCWS, 32 pCWS and 60 CWNS available for the proposed project. Participants in the proposed study will undergo further fluency assessment using the SSI-4 to confirm diagnoses and a series of behavioral tests has been used in Chang's study [4]. History of participants' fluency treatment will also be noted. According to Chang's study, children produce about 300 syllables during the proposed storytelling task (see C3.4). To allow for the possibility that scanner noise may reduce stuttering frequency by 25% on average [29], only pCWS whose stuttering frequency is >4.4% during a speech assessment in a quiet environment will be recruited. This will help to ensure that we can obtain >10 in-scanner stuttering

instances (4.4% x 0.75 x 300 syllables) for achieving Specific Aim 1b. In case a participant generate <10 in-scanner stuttering instances, he or she will be excluded from the fMRI analysis related to Specific Aim 1b.

C3.2 Scientific rigor. Based on Preliminary Study 4 (see C2.2), we assume that the proposed study will obtain an effect size of 0.7 with a standard deviation of 0.65 in the comparison between pCWS and CWNS in the brain activity associated with fluent speech production (Specific Aim 1a), and an effect size of 0.58 with a standard deviation of 0.74 in comparison between activity associated with stuttered and fluent speech in pCWS (Specific Aim 1b). With an alpha of 5% and power of 0.8, a sample size of 15 per group should suffice to observe a difference in both comparisons and potentially in the comparison between rCWS and CWNS (Specific Aim 2). However, considering a potentially higher exclusion rate of images or participants due to severe motion despite our de-noising technique and potentially smaller effect size comparing rCWS and CWNS, we plan to recruit an initial sample size of 20 per group. Additionally, several measures will be implemented to ensure robust and unbiased results: i) participants' speech assessments will be carried out by two independent speech-language pathologists to ensure reliable stuttering diagnoses and identification of stuttering instances, ii) fMRI data analysts will be blinded to participants' diagnoses to ensure unbiased group comparisons, iii) permutation procedures [37] will be used to control false positives related to multiple comparisons in fMRI analyses because false positives may not be controlled appropriately using other methods [38], and iv) details of diagnosis criteria, definitions of stuttering instances, experimental design, scanning parameters as well as analysis procedures will be fully explicated in any resulting publications to maximize study reproducibility.

C3.3 Equipment and hardware. Functional and anatomical images will be acquired with the latest generation GE 3T MRI scanner, MR750, with an 8-channel head coil at the fMRI Laboratory, [redacted]. Functional images will be acquired using a standard echoplanar (EPI) pulse sequence with the following key parameters: recovery time (TR) =2 sec; voxel size=3.45x3.45x4 mm; 38 interleaved sagittal slices; acceleration factor=2. Anatomical images (MPRAGE) with resolution of 1 mm^3 will be acquired at the end of the experiment. Speech during the fMRI experiment will be recorded with an optical noise cancellation microphone (OptoAcoustic) and a MR-compatible camera (MRC Systems) mounted on the scanner's head-coil. Timing of scanning acquisition, video/audio recordings and stimulus presentation will be synchronized using E-Prime 2.0 Professional (Psychology Software Tools, Inc.). Participants' hearing will be protected by noise-shielding headphones or earplugs. All required equipment is available for the proposed study. The same setup was used in Preliminary Study 4 presented in C2.2; for details of scanning parameters, see [5].

C3.4 Speech tasks during fMRI. The child's main speaking task is to tell a story guided by a textless picture book, "Frog, where are you?" to elicit continuous speech during fMRI [39]. This book portrays an age-appropriate story in 30 vivid pictures. This task has been successfully administered by our team to 120+ children (aged 3 to 11). To permit comparison of our results with children to similar studies of adults, we will include a control task, where children will produce overlearned speech (e.g., "A B C …") prompted by a picture. This task has been used as a baseline condition in brain imaging studies of speech production in adults (e.g., [40]) and as an assessment of childhood speech disorders [41]. Prior to scanning, participants will be familiarized with the experimental procedure. During scanning, story pictures will be presented via a projector sequentially with intermittent presentations of control task pictures. Each picture will be presented for 15 seconds, followed by a 10-second rest period. The entire fMRI experiment will be less than 15 minutes per participant.

C4 ANALYSES

C4.1 Speech data analysis. The Co-I Ratner's team will transcribe participants' speech and identify the precise onset times of stuttering instances using a text-based speech analysis software CLAN/CHAT [42]. We consider part-word or single-syllable-word repetitions and dysrhythmic phonations (i.e., blocks and prolongations) as *instances of stuttering*. The onset and offset of a stuttering instance will be determined by stuttered sound for repetitions and prolongations and observable lips movements (e.g., mouth open, lips trembling, etc.) for blocks. Onset and offset times of stuttering instances will be used for the fMRI analysis to identify their associated brain activity (Specific Aim 1b). Additionally, using the transcripts, individual linguistic measures including speech rate, utterance length, semantic diversity (e.g., TTR, VocD) and syntactic complexity (e.g., DSS, IPSYN) will be computed by CHAT. Along with other variables, they will be used as covariates in the fMRI analyses to control potential sources of variation for example [43].

C4.2 fMRI data analysis. Preprocessing steps include: i) slice timing correction, ii) head movement correction, iii) sICA de-noising, iv) normalization to a standard brain template, and v) spatial smoothing (see [5] for details). As in Preliminary Study 4 (see C2.2), functional images of each participant will be modeled using a mixed block/event-related design in GLM framework implemented in software SPM12 [23]. Specifically, our participants' speech and stuttering instances will be modeled by a block and an event regressors, respectively. Participants' first 2-3 principle components of the linguistic measures, stuttering severity, types of treatment received, intelligence quotient, socioeconomic status, and **biological variables** including sex and age will be

entered as covariates in the model. At the group level, individual model estimates (β) will be compared using *t*-tests. False positives due to multiple comparisons will be corrected by a permutation procedure [37].

Data analyses for Specific Aim 1. Identify brain activity associated with continuous speech production that characterizes persistent stuttering. The first data analysis will test the hypothesis regarding Specific Aim 1a (**H1a**) that brain activity of pCWS during fluent speech production differs from that of CWNS in cortical areas supporting speech monitoring. This analysis will compare individual estimates of fluent speech between pCWS and CWNS using two-sample *t*-tests. Results will reflect the neural characteristics associated with fluent speech segments in pCWS. The second analysis will test the hypothesis regarding Specific Aim 1b (**H1b**) that brain activity associated with instances of stuttering in pCWS, in contrast to their fluent speech, will differ in brain areas supporting motor planning and control. This analysis will compare individual model estimates of stuttering instances vs. fluent speech in pCWS using paired *t*-tests. Findings from this analysis will reflect pCWS's brain activity associated with instances of stuttering in addition to the activity during fluent speech segments. Overall, analyses associated with Specific Aims 1 should provide insights into the neural processes associated with persistent stuttering.

Data analyses for Specific Aim 2. Identify brain activity associated with continuous speech production that characterizes recovery from stuttering. The analyses will test the hypotheses regarding Specific Aim 2 that brain activity of rCWS during fluent speech production will differ from that of pCWS and CWNS. Specifically, **H2a**: rCWS, when compared with pCWS, are hypothesized to exhibit lesser anomalous activity in the left perisylvian regions and **H2b**: rCWS, when compared with CWNS, are hypothesized to exhibit increased activity in the right frontal areas. These analyses will compare individual estimates of fluent speech between rCWS and pCWS as well as rCWS and CWNS using two-sample *t*-tests. Findings are expected to reflect the neurological characteristics associated with rCWS. Overall, analyses associated with Specific Aim 2 should provide insights into the neural processes associated with recovery from stuttering.

C4.3 Potential problems and alternative approaches. The present proposal's hypotheses are mainly based on evidence from neuroimaging studies of continuous speech in adults or indirect evidence such as structural anomalies associated with children's stuttering persistence and recovery. First, although results from CWS and AWS appear to be converging, it is also possible that there are marked differences in brain activity between adults and children associated with stuttering and fluent speech production. If so, our hypotheses may need to be revised. Given that the proposed study would be the first attempt to examine brain functional differences during continuous speech production in CWS, we believe that even if the original hypotheses are in need of revision, the data obtained from this study will contribute novel and important information regarding neural bases of childhood stuttering. Second, extremely abrupt head movements exceeding the workable range of our de-noising method (>9 mm) may occur during our participants' speech production. It should be rare because movements of participants' heads are restrained. In case extremely abrupt head movements occur, in addition to our sICA de-noising, we will use a conventional technique called image scrubbing [19] to remove the affected fMRI volumes. Third, there is always a chance of data loss due to lack of compliance with the task by some children. This possibility is expected to be low because most of our potential participants will have already been scanned by our research group and performed the storytelling task several times successfully in the past. If a child does not perform the task correctly, or is not able to complete the experiment, we will attempt to reschedule the visit and provide extra training sessions for that child.

C5. TIMELINE

Month 1-18: Recruit participants, conduct fMRI experiments and prepare for data analysis to address hypotheses associated with the Specific Aims. **Month 12-24**: Analyze speech and fMRI data. Present preliminary findings at national and international conferences. Begin to prepare manuscripts. **Month 24-36**: Prepare and submit manuscripts to peer reviewed journals, respond to reviews, publish reviewed/revised manuscripts and present final results at national and international conferences.

C6. SUMMARY OF PROJECT/FUTURE DIRECTIONS

The outcomes of the proposed study are expected to further enhance our understanding of neural processes of continuous speech production associated with persistence and recovery of stuttering. Such understanding should be foundational to future investigations of how stuttering instances are initiated by tracking brain activity transitioning from fluent speech to the onsets of stuttering instances using time-resolved fMRI [44]. Moreover, to extend the proposed study, we plan to apply functional connectivity techniques to study interregional interactions during continuous speech production that characterize stuttering persistence and recovery [17]. Findings of the proposed study will also provide guidance for a future longitudinal study of CWS, in which we plan to track the neurodevelopment of speech production starting from CWS's stuttering onset to recovery/persistence to reveal early prognostic neural markers of recovery/persistence. Such a program of studies, we believe, will eventually assist in developing more effective treatment strategies for childhood stuttering.

PROTECTION OF HUMAN SUBJECTS

1. Risks to Human Subjects

1.1 Human Subjects Involvement, Characteristics, and Design

The proposed study will involve behavioral testing and brain imaging in a single visit of each participant. Approximately 72 school-age children from 5 to 11 years will be recruited from our ongoing longitudinal neuroimaging studies of childhood stuttering, in which more than 60 children who stutter and a like number of fluent control peers were drawn around [redacted], [redacted] and have been assessed annually in the last 3-4 years. Of 72, 24 will be persistent in stuttering, 24 recovered from stuttering, and 24 fluent controls who have never been diagnosed with stuttering nor have family history of stuttering. Recovery and persistence as well as no history of stuttering will be determined according to the most recent two annual speech-language assessments and parental reports of our ongoing longitudinal study. After ~15% attrition (maximum rate estimated from our ongoing longitudinal study) and potential data loss due to failure to complete experimental task, movement artifacts, and so forth (which may add another ~20% of data loss), around 16 samples in each of the three groups will be obtained.

Because the aim of the proposed project is to compare brain activity associated persistence and recovery of childhood stuttering, it is important to objectively identify children who persist in and have recovered from stuttering. Since the determination of persistence and recovery from stuttering is best accomplished at least 2 years after onset, children who stutter younger than 5 years of age will not be included in the proposed study. Composition of age, gender, and wherever possible, race, ethnicity, and social-economic status (using Hollingshead Four-Factor Index of Social Position) will be equated between the three groups. As the male-to-female ratio in stuttering prevalence is about 3 to 1, we expect that there will be more boys than girls, approximately 2-3 boys to 1 girl in each group. All participants will be monolingual English speakers without any diagnosed developmental or psychiatric disorders other than stuttering.

According to the recommendation of the Speech-Language Pathologist and the wishes of the parents or guardians, children with persistent stuttering or have recovered may receive treatment or no course of treatment. We expect that at least 25-50% of children who stutter in our sample, including those recovered, will have received therapy in the past.

Parents and/or caregivers will complete forms and/or answer questions about the child's behavioral, medical, social, and developmental states and speech, language and hearing background. All participants will undergo a standardized speech fluency assessment to confirm their group assignment and perform a storytelling task in the scanner. Parents or guardians will be in the adjacent interview or observation room or, if necessary, in the experimental testing room with the child if he/she is overly distressed at separation. During speech fluency assessments and brain imaging procedures, children will be audio-video recorded.

De-identified speech data recorded during brain imaging will be analyzed by Prof. Nan Ratner, Co-Investigator at the University of Maryland. She and authorized students and staff will access the data that are stored at the [redacted], i.e., the PI's host institution via password-

protected virtual private network (VPN) and encrypted remote control desktop connection. In this way, no data will be permanently transferred to the collaborator site.

1.2 Sources of Materials

This project involves four sources of research material: 1) Questionnaire data (e.g., intake screening form, developmental history, demographic information obtained from parents, behavioral questionnaires, etc.), 2) brain imaging data (e.g., structural image and functional MRI), 3) audio-video speech data during speech-language assessment and brain imaging, and 4) Behaviorally coded data (e.g., during testing, some behavioral observations will be coded by either paper-and-pencil means and/or subsequently through the use of computerized software e.g., frequency of stuttering-like disfluencies per task). All data will be stored in a locked filing cabinet or a password-protected computer housed in a locked room at the Rachel Upjohn Building, the [redacted], accessible only to the PI, Co-Investigators, and authorized students and staff. The participant's identity associated with all data files, either in paper or computerized format will be codified.

1.3 Potential risks

a. *Breach of privacy*. The risks involving breach of sensitive private information will be minimized by having all subjects' data de-identified and handled only by the PI and other authorized investigators. All investigators will receive human research protection training according to IRB guidelines of their host institutions. All subject data will be placed in individual coded files that will be locked in a cabinet or a password-protected computer housed in a locked room at the [redacted].

b. *Inconvenience or discomfort during behavioral testing*. All participants will be given breaks as needed, and will not be pressured to continue if there is excessive anxiety or fatigue. The testing sessions will be divided into 2 or 3 sessions as necessary.

c. *Inconvenience or discomfort during MRI scanning*. Well-known risks for MRI scanning involve the presence of ferromagnetic foreign objects in and/or on the body (e.g., pacemaker, surgical clip, staples, etc.), claustrophobia, as well as possible inconvenience or discomfort during the scanning due to the requirement of lying still, and exposure to loud noise. The risks involved in MRI participation are usually greatly minimized through a thorough screening procedure, followed by ample opportunity for exposure to the sights and sounds of the MRI setting. Discomfort due to loud noise during scanning will be minimized through use of earplugs, headphones, and padding around the head as well as the inside of the MRI bore. One staff member will sit next to the child during the length of the MRI session to monitor any discomfort. If the child shows any signs of discomfort or anxiety during the scanning, the procedure will be interrupted and stopped if necessary.

d. *Incidental MRI and/or behavioral findings*. Any MRI scans that appear to have potential clinical abnormality will be forwarded to a radiologist, and if confirmed abnormal, the findings will be communicated to the study investigator, who would notify the parents and, with permission, forwarded to the child's primary care physician as designated by the parents. Further referrals to appropriate clinicians would be made as appropriate. If, during the

behavioral assessments, it is found that the child has a clinically significant developmental delay, speech-language deficit, or a cognitive, learning, or behavioral problem, that information would be shared with the parents as well. The parents would be encouraged to contact the child's physician for follow-up and possible referrals to the appropriate professional for intervention.

2. Adequacy of Protection Against Risks

a. *Participant Recruitment*. Participants of the proposed project will be recruited from the participant pool of the ongoing longitudinal neuroimaging study headed by the co-investigator Dr. Soo-Eun Chang. This ongoing longitudinal study has recruited around 60 children who stutter and a like number of fluent control peers were drawn from [redacted] and have been assessed annually in the last 3-4 years, via advertisements in magazines and recruitment letters. Dr. Chang and her research team will make initial contacts with the potential participants' parents or guardians to inquire whether they are willing to participate in the proposed study.

b. *Consent to participate: Parents*. Consent to participate will be obtained from the parent(s) or guardian(s) of the child, and assent to participate will be obtained from the children. We will first obtain consent from the parent because 1) experience indicates that parents must agree, understand and be comfortable with participating before their child will be and 2) discussing these matters first, with the parent, allows the child a greater period of time to warm up to the study environment and to the investigators. Parents will read and sign an IRB-approved consent form in the presence of the PI, co-I, the Speech-Language Pathologist, or a doctoral-level project team member at the beginning of the visit. The parents/guardians will also be given a verbal overview of the project and any questions will be answered and concerns addressed. The parents/guardians will also be informed that they may ask questions at any time during the procedures and/or stop the procedures at any time during the assessment with no penalty. At the end of each assessment, the PI or Co-I or Speech-Language Pathologist will share testing results with the parents and answer any questions about the child's performance, results of testing, etc. If the PI, Co-I or Speech-Language Pathologist at the assessment finds that the child needs follow-up attention from another professional, he/she will make that recommendation at that time and provide resources for the parents to contact.

c. *Assent to participate: School aged children*. Once the parent(s) has/have consented, the PI, co-I, the Speech-Language Pathologist, or a doctoral-level project team member will obtain assent to participate from elementary school-age participants. If they are pre-readers and pre-writers, verbal assent will be obtained. For children who can read and write, we have created a child assent form that they may sign. Obtaining assent from children involves slow, clear and repetitive explication to the child of what we will do and what he or she will need to do in response (usually quite simple, e.g., storytelling assisted by pictures or having a conversation). We ask the child if he or she understands what we will do and if it is okay. We make clear that we will take breaks and stop whenever the child wants. In our experience, less than 1% of children that we initially test do not appear to understand the above instructions after three attempts to explain them to him or her, and if this is the case, the child is not a viable candidate for our work and is excluded from further consideration. All investigators and project members

are or will be trained in appropriate IRB-approved procedures required by the [redacted]

d. *Protection against risks*. Risks in participating in standardized testing, videotaping of speech, and MRI imaging are minimal. To minimize the risks, we will, before each assessment begins (as explained above), thoroughly explain all procedures to both parent/guardian and child. Also, as suggested above, ample time will be allowed, during such explanation, and throughout testing, for parents/guardians and children to ask questions about procedures, goals, and methods. Written consent forms, that have first been verbally described, will be presented to the parents/guardians for their review and signature. Verbal or written assent will be obtained from school-age children in the presence of their parents. Before brain imaging experiment starts, a thorough screening procedure will be carried out to minimize the risks involved in MRI participation.

At any time during any assessment, the parents/guardians and/or children can end the session without penalty. If children become upset, we will stop and allow parents to soothe them. Breaks will be used to minimize child fatigue and frustration. Parents will stay in the next room to their child throughout testing, or in the same room if the child has difficulty separating. Families will be reimbursed for their participation, effort, time, and travel to assist them with costs and inconvenience to their schedules. Resulting test scores, performance during experimental testing, etc. associated with each participant will be, as discussed above, stored in locked cabinets or password-protected computer in a locked room at Rachel Upjohn Building, the [redacted]. A non-identifying code will be assigned to each participant for organizing the participant's coded and statistically analyzed data files.

3. Potential Benefits of the Proposed Research to the Subject and Others

Risk to benefit ratio. The risks of fatigue, discomfort, and disruption in family schedules are outweighed by the benefits received. Indeed, without any financial charge to the family, the parents of children will be informed of results based on state-of-the-art speech and language testing of their child, and MRI evaluation of the child's brain, testing that would cost thousands of dollars if done in a typical clinical setting. Such information is particularly salient for some parents whose children are known or suspected to stuttering as well as parents who are curious about the speech and language development of their children. From the experience obtained from our ongoing longitudinal neuroimaging study, participation in the project has intrinsic value to most parents in terms of learning more about their child. In sum, it is our experience that many parents are not merely participating to "help science," they are participating to better understand their child and his or her performance, which suggests that the information obtained in this project has more than a little benefit for many families.

4. Importance of the Knowledge to be Gained

Results from this project are expected to increase our understanding of neural activity associated with persistence and recovery from childhood stuttering. This knowledge will bring us one step closer to a more comprehensive understanding of the neural processes of continuous speech production and how these processes are disrupted, leading to instances of stuttering. This has potential to provide an objective neural marker for evaluating persistence/recovery of

childhood stuttering and effectiveness of therapeutic strategies or treatments. Thus, benefits from this project - advancement of our understanding and possible improvements in assessment/treatment of stuttering - would seem to outweigh the minimal risks involved to participants. This is particularly so when one weighs, on the one hand, the significant negative impact that stuttering has on the academic, emotional, social, and vocational achievements, development and potential of individuals who stutter and, on the other, the very minimal risks to the child and parents/guardians by having them participate in this project. Additionally, considering stuttering has a significant negative impact on the quality of life of people who stutter, knowledge derived from this project would appear to far outweigh the minimal risks involved to participants. In sum, minimal risks to participants that may occur are more than reasonable given the society's strong need for understanding and treating stuttering.

Inclusion of Women

Children of both genders are included in this proposal. We will strive to have balanced numbers of girls and boys in each group in order to analyze potential gender effects. Although girls are under-represented in samples of children with stuttering, we will make every effort to include girls in the proportion they occur in the population with this disorder (boys to girls ratio: 3:1). In the subject pool of our ongoing neuroimaging study of childhood stuttering, in which the participants will be recruited from, the ratio of boys to girls who stutter is 1.7:1. We expect to be able to recruit a similar ratio of boys and girls in the proposed project period.

Inclusion of Minorities

We anticipate including minorities in approximately the proportions found in the regional population (about 81% White). To maintain the representativeness of our samples, ethnic composition of the proposed project will be monitored periodically. Because there is a tendency for low income and African American families to live further from campus, transportation costs will be provided to enhance recruitment of those families if necessary. No participant will be excluded because of minority status. Because some tasks are language based, it is scientifically necessary that all participants are native English speakers.

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: Neural markers of persistence and recovery from childhood stuttering: An fMRI study of continuous speech production

Domestic/Foreign: Domestic

Comments:

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	**0**
Asian	0	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	7	11	0	0	**18**
White	18	33	0	0	**51**
More than One Race	0	0	1	2	**3**
Total	**25**	**44**	**1**	**2**	**72**

Study 1 of 1

Funding Opportunity Number: PAR-16-057. Received Date: 2016-02-23T15:48:23.000-05:00

Inclusion of Children

The current proposal includes children from ages 5-11. Including children is necessary because the research focuses on the neural processes associated with persistence and recovery from childhood stuttering. Questions about persistence and recovery from childhood stuttering cannot be studied without including children in the research. The project team has extensive experience working with children in this age range. The Co-I Dr. Soo-Eun Chang is licensed and experienced clinicians (speech-language pathologist, neuropsychologist), who will be available on call.

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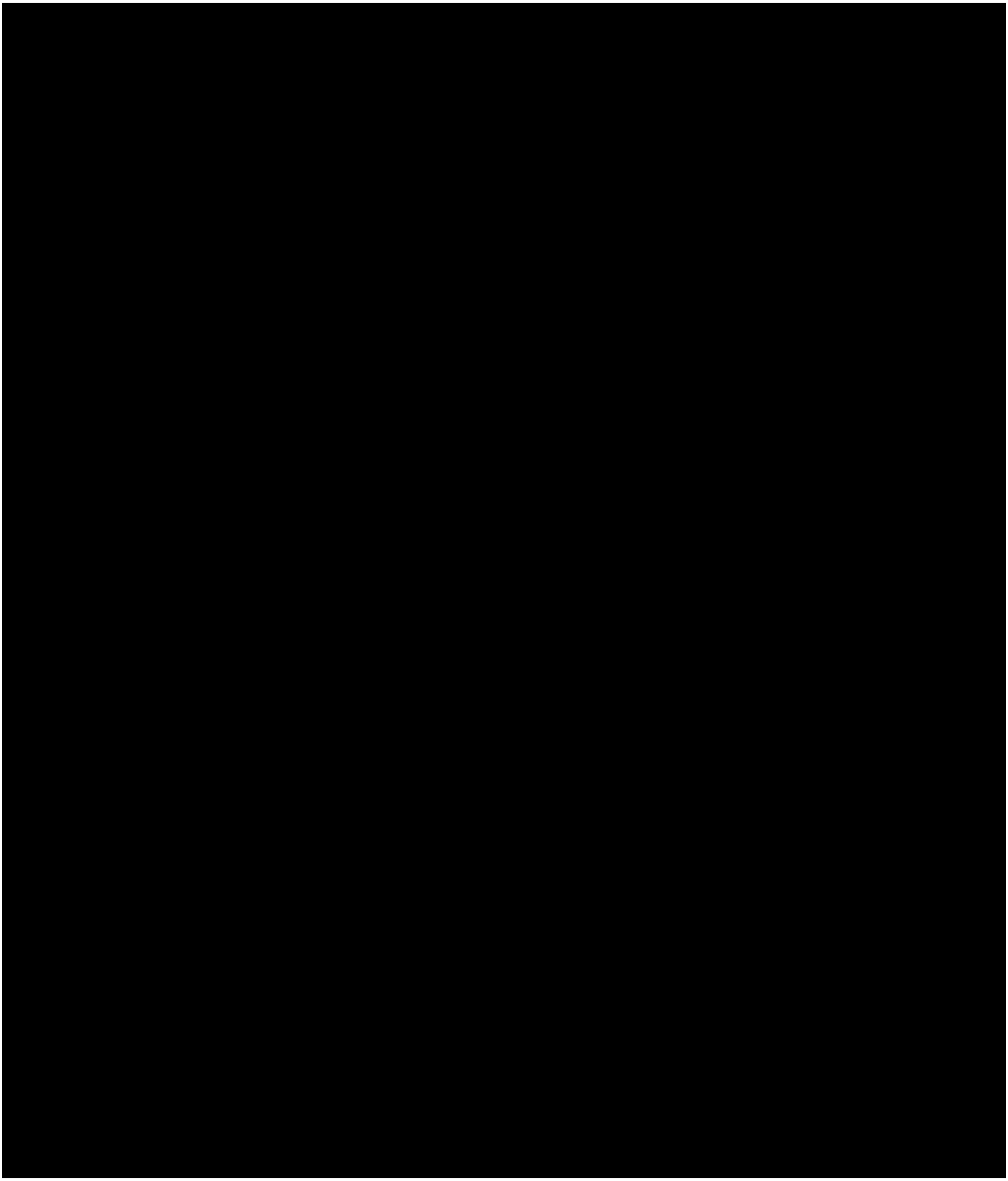

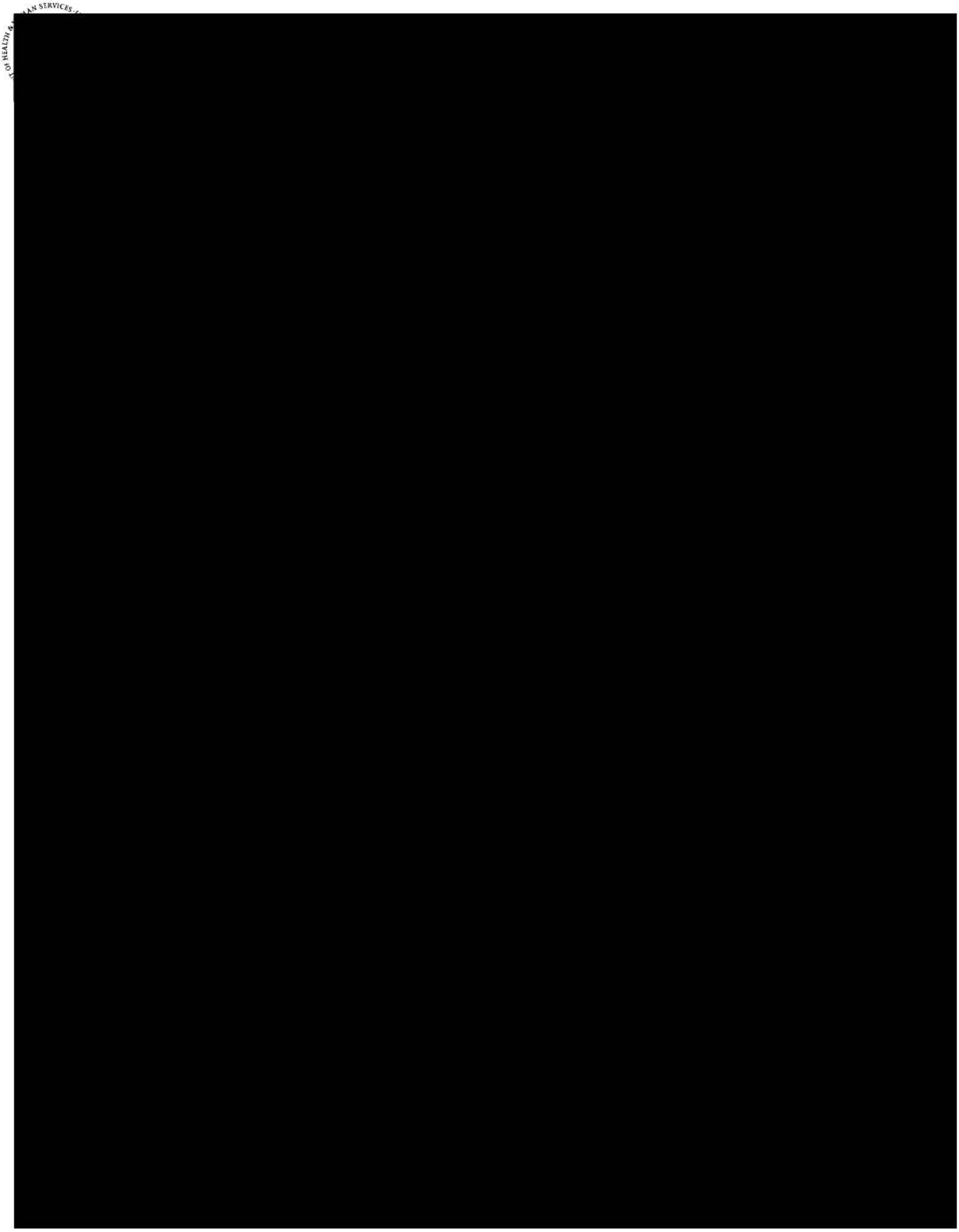

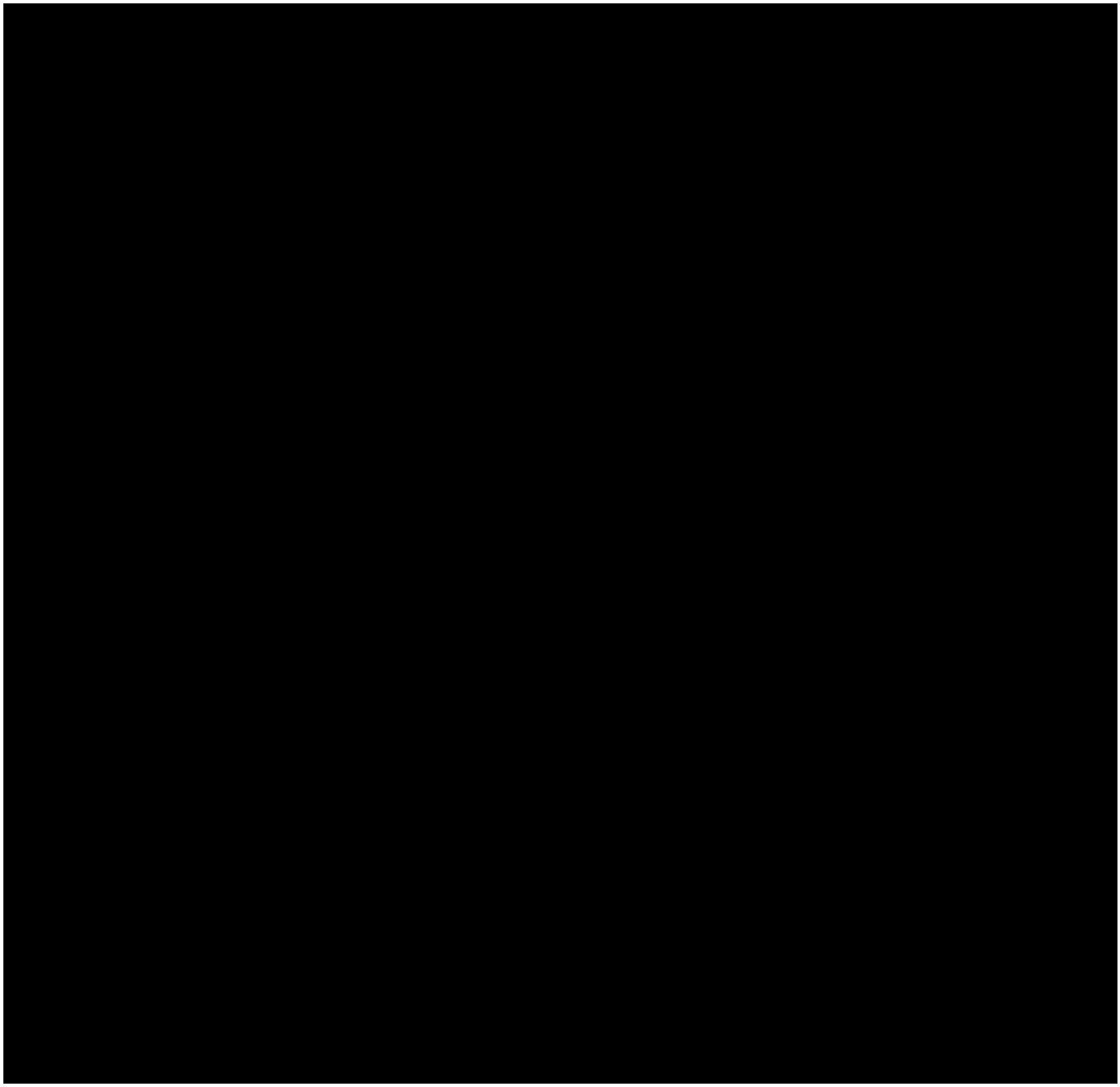

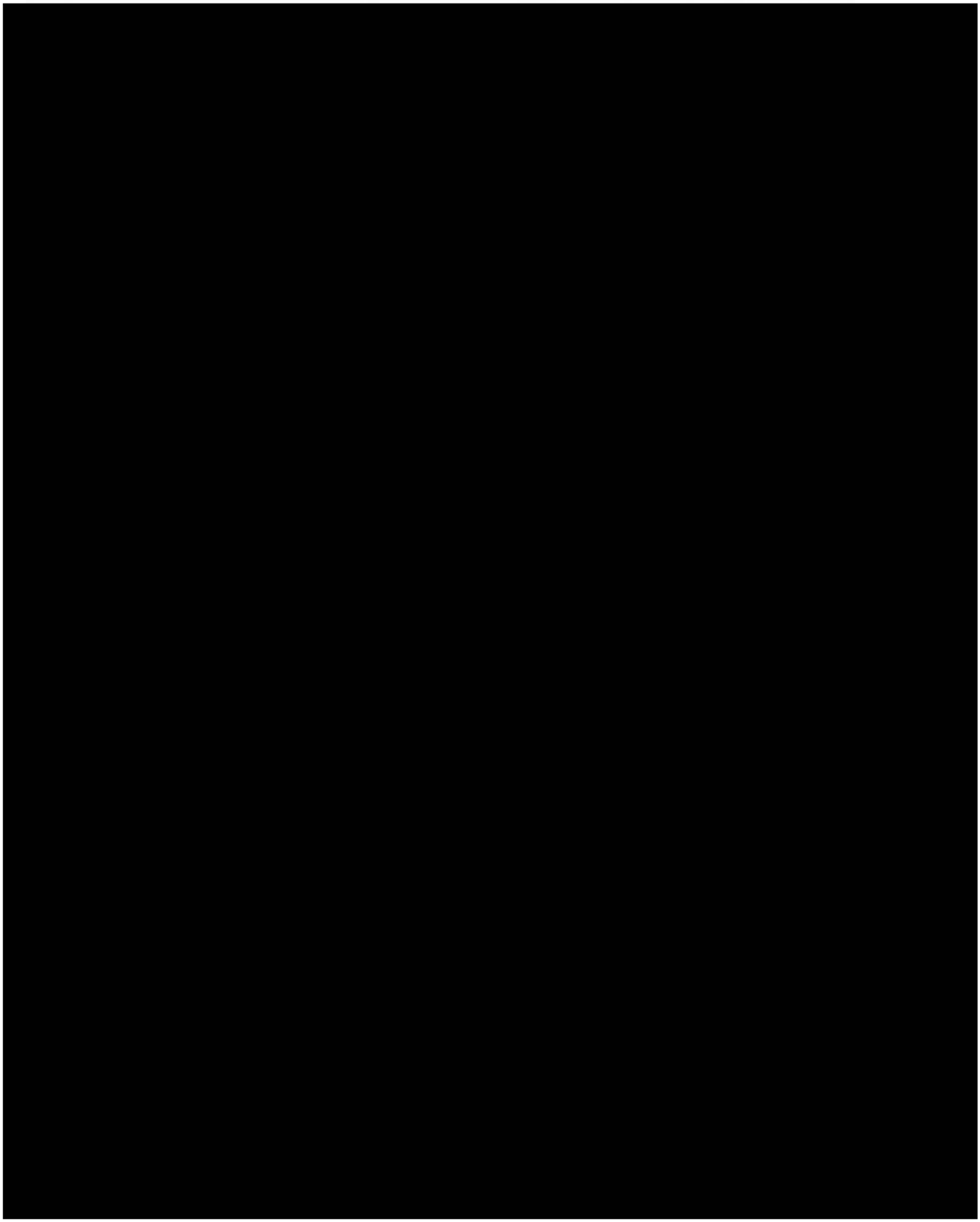

RESOURCE SHARING PLAN

a) Data sharing plan

Data will be shared in a timely and collegial manner. Once data analysis is completed and the manuscripts addressing the specific aims of the proposed study are accepted for publication, data sets created in this research program will be made available for other qualified researchers upon request for purposes of scientific investigations or review. We anticipate that the data will be made available within one year after the study closeout date. While making these data as freely available as possible, privacy of participants will also be protected. Before distribution, the data will be de-identified, and only those relevant to the request will be provided. Investigators who request for the data need to sign a formal data-use agreement. Depending on the data types requested, data will be sent to the investigator by mail or secure transfer.

b) Sharing model organisms.
No applicable

c) Genome-Wide Association Studies
Not applicable