SUMMARY STATEMENT

PROGRAM CONTACT: [redacted]

(Privileged Communication)

Release Date: **07/22/2016**
Revised Date:

Application Number: **1 R21 DC015853-01**

Principal Investigator

CHOW, HO MING

Applicant Organization: [redacted]

Review Group: **CDRC**
Communication Disorders Review Committee

Meeting Date: **06/23/2016**
Council: **OCT 2016**
Requested Start: **09/01/2016**

RFA/PA: **PAR16-057**
PCC: **VS02**

Project Title: **Neural Markers of Persistence and Recovery from Childhood Stuttering: An fMRI Study of Continuous Speech Production**
SRG Action: **Impact Score:20**
Next Steps: **Visit http://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **30-Human subjects involved - Certified, no SRG concerns**
Animal Subjects: **10-No live vertebrate animals involved for competing appl.**
Gender: **1A-Both genders, scientifically acceptable**
Minority: **1A-Minorities and non-minorities, scientifically acceptable**
Children: **2A-Only Children, scientifically acceptable**

Project Year	Direct Costs Requested	Estimated Total Cost
1	[redacted]	[redacted]
2		
3		
TOTAL	[redacted]	[redacted]

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.
ADMINISTRATIVE NOTE

1R21DC015853-01 Chow, Ho Ming

RESUME AND SUMMARY OF DISCUSSION: This application for an NIDCD Early Career Research (ECR) Award (R21) seeks three years of support for Dr. Chow to determine brain activity patterns associated with continuous speech production in children with persistent stuttering and children who recovered from stuttering. Strengths of the application include the potential impact of the research, which could lead to treatments for persistent stuttering, and the PI, who participated in the development of the experimental method of de-noising motion artifacts in fMRI scanning. While preliminary data and data on head movements come from experiments with adults, this application proposes to apply the method to children who stutter, and is an interesting approach. The study represents the next step in investigating brain function during natural speaking in normal and clinical populations. The hypotheses are well articulated, the experimental design is well thought through, and the approach is rigorous and feasible.

DESCRIPTION (provided by applicant): 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.

PUBLIC HEALTH RELEVANCE: 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.

CRITIQUE 1:

Significance: 1
Investigator(s): 3
Innovation: 1
Approach: 3
Environment: 1

Overall Impact: The study aims at (1) understanding brain function during fluent and disfluent continuous speech in children who stutter and (2) capturing differences between those with persistent stuttering and those who recover from stuttering. The study addresses a very important research topic and represents the next step in studying brain function during natural speaking in normal and clinical populations. The PI was trained in the lab where the method for recording and analyzing fMRI during continuous speaking was developed; he took part in the process of its development (a co-author on a methodological paper). The PI appears to be the first to implement this method with a stuttering population. He appears to have great support through his collaborators and at the institution. Overall significance of this research and innovation are very high and there are no concerns regarding the PI's level of technical expertise and team support to deliver the results. There are few minor methodological questions, but they do not affect the overall enthusiasm for this project.

1. Significance:
Strengths

- Being able to examine brain function during fluent and disfluent continuous speech is very exciting. The development of the method to do so is very timely as it is a natural next step in the progression of an investigation into the brain of those who stutter (and hopefully other clinical populations in the future).
- Scientific premise for this line of research has been sufficiently well presented.
- Examining the differences in the brain function of those who stutter and those who recovered from stuttering is very promising as well as it may lead to the development of a predictive marker of stuttering recovery and lead to the subgrouping of the children early on with clear implications to speech therapy planning etc. The clinical implications are described very realistically in the application.

Weaknesses

- None

2. Investigator(s):
Strengths

- PI – appropriate, diverse background in engineering and neurosciences (neurolinguistics); Postdoc at NIDCD with mentor (Allen Braun) who developed the fMRI de-noising technique.
- PI – NIH award for research excellence
- Great and appropriately assembled team, which includes Allen Braun; Soo-Eun Chang – who leads a large and productive research group at [redacted] with research focus on stuttering; and Nan Bernstein Ratner – who is an expert in the analysis of speech of stutterers.
- Although Allen Braun was the post-doc mentor, his involvement is justified by the novelty of the fMRI method, which will be central to the study.

Weaknesses

- PI's productivity to date (since 2009) – only moderate – 4 first-author pubs (in imaging journals, which is great); 4 other pubs. No history of previous funding.

3. Innovation:

Strengths

- A novel (published) method of fMRI data de-noising will be used for the first time in children who stutter.
- Continuous speech will be studied in order to elicit stuttering events.

Weaknesses

- None.

4. Approach:

Strengths

- Access to a large pool of participants who are already part of ongoing research (R01) and familiar with the overall procedures (MRI) and task (story telling); the recovered stutterers are also known, which is a significant strength.
- A validated fMRI de-noising method
- Connected speech task to elicit disfluencies
- Clearly described preliminary works
- Well stated hypotheses
- Connected speech measures collected, analyzed and used as co-variates.
- Well defined inclusion criteria with provisions around stuttering severity
- Nice estimate of stuttering events in the MRI

Weaknesses

- It would have been nice to see pilot data (or maybe someone published this) on the head movement characteristics during stuttering event in either kids or adults (In a scanner with head restrain if possible). This issue, however, is dealt with appropriately in “limitations”.
- Limited details on the screening of participants – language testing/ IQ testing etc.
- Would parents agree on an additional fMRI session for kids that are already in the study or will this recording be a part of the other data collections?
- Not sure how the “normal” dysfluencies will be handled

5. Environment:

Strengths

- Sufficient institutional support
- Appropriate laboratory resources
- Appropriate resources at the University of Maryland

Weaknesses

- None

Protections for Human Subjects: Acceptable Risks and/or Adequate Protections

- well described Protection of human subjects; numbers are justified; risks are minor and justified

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion of Children under 18: Including ages <18; justified scientifically
- the study is about childhood stuttering; inclusion of children is justified; risks are small

Vertebrate Animals: Not Applicable

Biohazards: Not Applicable

Select Agents: Not Applicable

Resource Sharing Plans: Acceptable

Authentication of Key Biological and/or Chemical Resources: Not Applicable

Budget and Period of Support: Recommend as Requested

CRITIQUE 2:

Significance: 2
Investigator(s): 2
Innovation: 2
Approach: 2
Environment: 2

Overall Impact: This is a well-designed application that seeks to understand brain mechanisms contributing to either recovery from, or persistence of, stuttering in children. There is significant potential knowledge to be gained in understanding recovery from, as opposed to persistence of, stuttering in children, which could ultimately lead to improved, data-driven treatments for persistent stuttering. The team includes seasoned pioneers in investigating the behaviors and neuroscience of normal and disordered speech and language and many of them have already worked together in productive collaborations. The main weakness is in the risk that assumptions driving the experimental design and analysis are based on pilot work acquired from adults who stutter, wherein mechanisms may not be the same; however, at the risk of having to implement alternative methods, the distinction between mechanisms underlying adult and childhood stuttering would also be important to understand. The likelihood for the project to exert a significant and sustained impact on the study of childhood stuttering and potentially other developmental communication disorders is high, especially if the team succeeds in demonstrating the reliability of this novel fMRI analysis technique in children who stutter.

1. Significance:
Strengths

- Although advances have been made in understanding speech-motor control brain circuitry and its breakdown in adult stuttering, very little is known about speech-motor circuits in children who stutter (CWS) and those who don't (CWNS).
- This study will improve our understanding of brain mechanisms that underlie both persistence of and recovery from stuttering.
- If its aims are met, the study results could lead to a biomarker that dissociates persistent from recovered stuttering, potentially aiding in the development of new, targeted interventions aimed at preventing the development of persistent stuttering.
- If successful, this project will not only demonstrate the feasibility of using fMRI to study continuous speech production in persistent (p) and recovered (r)CWS and CWNS, it will also lead to new ecologically valid applications of the de-noising methodology in neuroimaging studies of other communication disorders across the lifespan.

Weaknesses

- None noted by the reviewer

2. Investigator(s):
Strengths

- The PI brings extensive expertise in fMRI acquisition and analysis of continuous speech in healthy and disordered populations.
- This is a strong team that includes pioneers in the fields of brain-language neuroscience (Braun), language and fluency across the lifespan (Ratner), and neural bases of pediatric stuttering (Chang). Many of them have already worked together in productive collaborations

Weaknesses

- None noted by the reviewer

3. Innovation:

Strengths

- If successful, the use of fMRI de-noising techniques, in part developed by the PI, will allow for examination of the brain during continuous speech production with vastly reduced motion artifact
- Investigation of stuttering and fluent speech in pCWS, rCWS, and CWNS during continuous speech production provides ecological validity since stuttering is more likely to occur during continuous speech-language planning and production, i.e., at the sentence and discourse level
- Study of brain mechanisms supporting fluent speech production in children who have recovered from stuttering has not been done before
- Mixed block/event fMRI design allows investigators to characterize patterns of fluent and dysfluent speech within children with persistent stuttering, as well as to characterize differences between fluent speech patterns in children who have recovered vs. those with persistent stuttering.

Weaknesses

- Being the first to investigate brain mechanisms underlying fluent and dysfluent connected speech production in children using fMRI, the project risks that their assumptions regarding similarities between children and adults are invalid.

4. Approach:

Strengths

- Use of fMRI (vs fNIRS) allows for whole brain interrogation, including subcortical regions involved in speech-motor circuitry; fMRI also has superior spatial resolution to fNIRS and is non-invasive (unlike PET).
- Use of spatial independent component analysis (sICA) in fMRI data analysis to separate motion artifacts from neuronally correlated signals allows for the study of continuous speech production, the most likely context in which to elicit stuttering
- The PI and team have demonstrated feasibility of removing motion artifacts related to head movements in children without discarding true BOLD signal. They also demonstrated feasibility of collecting fMRI during continuous speech in an 8-year-old child, with results similar to their prior findings in adults re: perisylvian activity for storytelling vs. automatic speech.
- Preliminary structural and functional MRI studies of persistent and recovered adults who stutter support the model-driven hypotheses in their specific aims

Weaknesses

- The application acknowledges a potential issue with assuming that brain activity in children who stutter will resemble that of adults who stutter.
- 8-channel head coil is not state-of-the-art but should be adequate for the task
- Could there be an issue with the fact that these children have been tested on multiple occasions with the same stimuli, i.e., that some of what accounts for the right hemisphere activity compared to CWNS is an effect of practice or overlearned speech?

5. Environment:

Strengths

- There is sufficient lab, office, and clinical space to support the research program
- Co-I Chang contributes a significant database of children who stutter or have recovered from stuttering and have already been studied longitudinally
- The neuroimaging facility includes required peripheral equipment to successfully perform the study, including the FOMRI-III optical noise cancelling system, and a mock scanner for participant training.
- Co-I Ratner contributes inclusion of continuous speech data from CWS and (recovered) CWDS to the TalkBank registry and provides use of CLAN/CHAT text-based speech analysis software which enables computation of diverse linguistic measures above and beyond fluency as well as comparison to other groups
- The Dept. Chair has expressed full support of Dr. Chow's proposal

Weaknesses

- None noted by the reviewer

Protections for Human Subjects: Acceptable Risks and/or Adequate Protections

- Research Strategy calls for 3 groups of 20 participants but Planned Enrollment Report states 72 participants

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion of Children under 18: Including ages <18; justified scientifically

Vertebrate Animals: Not Applicable

Biohazards: Not Applicable

Select Agents: Not Applicable

Resource Sharing Plans: Acceptable

Authentication of Key Biological and/or Chemical Resources: Not Applicable

Budget and Period of Support: Recommend as Requested

CRITIQUE 3:

Significance: 2
Investigator(s): 1
Innovation: 1
Approach: 2
Environment: 1

Overall Impact: This is an interesting R21 proposal to identify differences in neural activity and circuitry between children who recover from stuttering versus those who have persistent stuttering, using continuous speech in a novel fMRI paradigm. They hypothesize that children with persistent stuttering, like adults who stutter, will show reduced activation of normal perisylvian cortex activation (left IFG, STG) and increased activation of subcortical structures. Those who recover from stuttering may show increased activation of right IFG (based on some structural connectivity data they have obtained). What

they do not really discuss is the implications of the findings, if confirmed. The results could suggest differences in the brain that permit (lead to) recovery from stuttering, or simply reflect the effect of recovery.

1. Significance:
Strengths

- Stuttering is common and disabling, and can be persistent. It is not well understood why it persists in some children and not others.

Weaknesses

- There is brief mention that the research once accomplished would lead to treatment, but it is not clear how the findings would constrain treatment

2. Investigator(s):
Strengths

- Dr. Chow is an accomplished investigator in neuroimaging of language.
- He has recruited Dr. Chang and Dr. Bernstein-Ratner, who are leading experts on stuttering, to make up for his own limited experience in the area of stuttering research.
- Dr. Braun also complements the team with expertise in the neural basis of broad range of disordered and normal language and speech processes, especially during continuous speech production (as proposed here)

Weaknesses

- Dr. Chow has very little research experience in the domain of stuttering. He is the middle author of one published paper.

3. Innovation:
Strengths

- The idea, to identify neural circuits where activation and connectivity differ between children who have persistent versus recovered stuttering, seems sound and unique.
- The fMRI paradigm has been used before by this group, but is relatively unique to their group.
- Although others have studied the neural basis of stuttering, this is a new approach with fresh hypotheses

Weaknesses

- Applying to children the method developed with adults does not seem that innovative. However, given the preliminary data, it might have been an appropriate R01 application.

4. Approach:
Strengths

- Rigor: Sufficient detail is provided in the scientific method to replicate the studies. Biological variables are accounted for
- Transparency: The premises are clear and justified

Weaknesses

- Rigor: the power analysis assumes an effect size obtained from preliminary studies with adults. While this is understandable (they have no preliminary data from fMRI with children) the effect sizes might be smaller in children, who tend to have more variable fMRI results than adults. This is a minor weakness.

5. Environment:
Strengths

- [redacted] clearly has all the resources available to conduct the research

- There is an existing population of children with history of stuttering (some of whom who have recovered) that has already been followed annually for a few years.

Weaknesses

- None

Protections for Human Subjects: Acceptable Risks and/or Adequate Protections

- The main risk is privacy and discomfort of scanning. There is no mention of possible risk of drawing attention to their stuttering. Children will provide assent.

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion of Children under 18: Including ages <18; justified scientifically
- Only children; an effort will be made to recruit more minorities by providing transportation

Vertebrate Animals: Not Applicable

Biohazards: Not Applicable

Select Agents: Not Applicable

Resource Sharing Plans: No Reviewer response

Authentication of Key Biological and/or Chemical Resources: Not Applicable

Budget and Period of Support: Recommend as Requested

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS: ACCEPTABLE
The protocol features minimal risk to subjects and employs adequate protection against risks.

INCLUSION OF WOMEN PLAN: ACCEPTABLE
Due to the prevalence of rate of stuttering, this study will recruit more boys than girls. An effort will be made to test an equal number of boys and girls.

INCLUSION OF MINORITIES PLAN: ACCEPTABLE
There is no information on whether the prevalence of stuttering varies according to race and ethnicity. Minorities will be included in the proportion found in the regional population.

INCLUSION OF CHILDREN PLAN: ACCEPTABLE
The study is aimed at children ages 5-11, which is scientifically justified.

VERTEBRATE ANIMAL: Not Applicable (No Vertebrate Animals)

BIOHAZARD COMMENT: Not Applicable (No Biohazards)

SELECT AGENTS: Not Applicable (No Select Agents)

SHARING RESEARCH DATA: Acceptable plans

ADMINISTRATIVE NOTE: Non-compliant Biosketches
During the review of this application, reviewers and/or NIH staff noted that one or more biosketches did not comply with some elements of the required format (NOT-OD-15-032). The requirements are as follows:
Briefly describe up to five of your most significant contributions to science. For each contribution, indicate the historical background that frames the scientific problem; the central finding(s); the influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology; and your specific role in the described work. For each of these contributions, reference up to four peer-reviewed publications or other non-publication research products (can include audio or video products; patents; data and research materials; databases; educational aids or curricula; instruments or equipment; models; protocols; and software or netware) that are relevant to the described contribution. The description of each contribution should be no longer than one half page including figures and citations. Also provide a URL to a full list of your published work as found in a publicly available digital database such as SciENcv or My Bibliography, which are maintained by the US National Library of Medicine.
Some of the biosketches do not include an URL to a full list of publications, or have more than 4 references per contribution.

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 1 R21 DC015853-01; PI Name: Chow, Ho Ming

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER
Communication Disorders Review Committee

NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

CDRC
06/23/2016 - 06/24/2016

CHAIRPERSON(S)

[redacted]

MEMBERS

[redacted]

[redacted]

MAIL REVIEWER(S)

[redacted]

SCIENTIFIC REVIEW OFFICER

[redacted]

[redacted]

[redacted]

* Temporary Member. For grant app cat ons, temporary members may part c pate n the ent re meet ng or may rev ew on y se ected app cat ons as needed.

Consu tants are requ red to absent themse ves from the room dur ng the rev ew of any app cat on f the r presence wou d const tute or appear to const tute a conf ct of nterest.