

Speech Processing in Stuttering

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Study Title: Speech Processing in Stuttering

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Objective

The proposed study addresses an important but understudied aspect of developmental stuttering pertaining to temporal aspects of auditory motor integration. Using behavioral speech and nonspeech synchronization tasks, the results are expected to provide a foundation for future large-scale studies that clarify neurophysiological correlates of auditory-motor synchrony examined in the study. Ultimately, the results obtained from these investigations may lead to developing treatments that are informed by a greater understanding of the neurophysiological bases of stuttering.

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1. Specific Aims

Aim 1. Compare implicit speech synchronization between adults who stutter and fluent peers. *H1a*: Fluent speakers will exhibit the expected bimodal distribution of good and poor synchronizers. ***H1b*:** AWS will exhibit poorer synchronization than fluent adults.

Aim 2. Compare implicit speech synchronization with explicit speech and non-speech synchronization in adults who stutter and fluent peers. *H1a*: If AWS have a general deficit in synchronization, AWS will show poorer synchronization in speech and non-speech tasks compared to fluent

adults. **H1b:** Alternatively, if AWS have a selective deficit in synchronization that is limited to speech, then AWS will show poorer implicit and explicit speech synchronization compared to fluent adults. **H1c:** Finally, if poorer synchronization in AWS reflects an implicit effect (i.e., spontaneous tendency) that can be overcome with explicit synchronization instructions, then AWS will show poorer implicit, but not explicit speech synchronization, compared to fluent adults; no difference between AWS and fluent adults is to be expected in non-speech synchronization tasks.

Aim 3 (exploratory). Compare implicit speech synchronization in children who stutter and fluent peers. We will extend the SSS paradigm to (a) establish feasibility and response distribution in fluent children, and (b) compare implicit speech synchronization between CWS and fluent children.

2. Significance & Background

Stuttering affects 3 million Americans and severely impacts verbal communication beginning in early childhood. Stuttering is challenging to treat, and traditional treatment yields varying results that often fail to transfer beyond the therapy setting. Efforts to understand its pathophysiological bases increasingly link stuttering to abnormal neural network structure and function in cortical speech-motor and auditory areas, and their connections with subcortical structures. This cortical-subcortical network crucially supports fine-grained control of internally timed and precise motor movements required for fluent speech production and overlaps with a rhythm processing network. Disconnect between speech-motor and auditory brain regions is a critical tenet of neurobiological models of speech production that propose stuttering results from poor auditory-motor integration, a failure of interareal synchronization between speech-motor and auditory brain regions. It is well established that speaking with external rhythmic pacing (e.g., metronome, choral speech) not only temporarily eliminates stuttering, but is associated with ‘normalized’ brain activity in speech-motor and auditory brain regions. This immediate induced fluency effect suggests that stuttering results in part from a deficient internal timing system that can be overcome with an externally driven pacing signal, whereby interareal synchrony between speech-motor and auditory brain regions is strengthened. One step towards novel, neuroscience-based treatments derived from a thorough understanding of this abnormal neural circuitry is first to measure auditory-motor synchrony in adults who stutter (AWS) and fluent speakers. To do this, we will use an innovative spontaneous synchronization of speech (SSS) task shown to index temporal dynamics of auditory-motor integration in fluent adults via implicit speech synchronization. In the SSS task, fluent adults continuously repeat “tah” while listening to an isochronous sequence of syllables. Despite no explicit instruction to align their production with the audio, some individuals spontaneously synchronize their production to what they hear, yet others are not influenced by this external pace. In fact, over a series of replication studies, speakers repeatedly exhibited a striking bimodal distribution of ‘good’ and ‘poor’ synchronizers. Moreover, good synchronizers showed increased brain to stimulus synchrony and structural connectivity of speech-motor and auditory regions. Here, we will use the simple yet powerful SSS task as a window through which temporal dynamics of auditory-motor integration can be measured in AWS. We will also compare implicit speech synchronization with explicit speech and nonspeech synchronization to explore timing and rhythm more broadly. Finally, we will extend the SSS task to children who stutter (CWS). While reduced auditory-motor integration has been shown in AWS using auditory perturbation and adaptation paradigms, this has been understudied in CWS, who have not developed compensatory responses to stuttering.

3. Method

3.1. Subject Recruitment and Screening

Most of the participants to be recruited for this study will be from existing participant pools (i.e., cross enrollment from other ongoing research studies within our labs) at MSU and UM while others will be newly recruited. The PI and Co-I Chang have established large recruitment databases for both adults (n~100) and children (n~250) who stutter and their fluent peers over the past decade, thus recruitment will primarily occur from within these pools. Participants enrolled in our past and current studies provide consent to be contacted about new studies. Additional recruitment will be achieved by reaching out to previous participants who meet the eligibility criteria, posting recruitment flyers in the area and posting on Reddit. To date, we have successfully recruited a sample that is representative of the US population with respect to socioeconomic status and race/ethnicity.

Once initial contact has been established with a participant/family that expresses interest in participating in our study, a member of our staff will explain via a telephone call, Zoom meeting, or in person if permitted, the purpose, procedures, and risks of the study in non-technical language. During the phone interview, a screening questionnaire will be conducted to ensure that the participant meets all study criteria. Participants will be interviewed to obtain information on their medical and general speech history, as well as family history of stuttering, stuttering onset, and development. We will also ask questions about their musical training experience. Once it is determined that the individual meets all basic inclusion criteria of the study, they will be brought in for the study.

3.2. Participants

Adults. 50 AWS and 50 controls between the ages of 18-65 will participate in this study, though up to 500 subjects may be recruited/screened to account for disqualifications, attrition, etc.

Inclusion criteria: adults who do not stutter

- Aged 18-65 years
- English as primary language
- Normal speech, language, hearing, cognition

Exclusion criteria: adults who do not stutter

- Personal or family history of stuttering
- Currently taking medication that affects brain function
- Major medical or psychiatric illness

Inclusion criteria: adults who stutter

- Aged 18-65 years
- English as primary language
- Normal speech, language, hearing, cognition (other than stuttering)
- Currently stutters

Exclusion criteria: adults who stutter

- Currently taking medication that affects brain function
- Speech therapy within the past year
- Major medical or psychiatric illness

Children. 40 children (30 controls, 10 CWS) between the ages of 6 to 17 will participate in this study though we may recruit up to 200 children to account for disqualifications, attrition,

Inclusion criteria: children who do not stutter

- Aged 6 to 17 years
- English as primary language
- Normal speech, language, hearing, cognition

Exclusion criteria: children who do not stutter

- Personal or family history of stuttering
- Currently taking medication that affects brain function
- Major medical or psychiatric illness
- Language/motor delay

Inclusion criteria: children who stutter

- Aged 6 to 17 years
- English as primary language
- Normal speech, language, hearing, cognition (other than stuttering)
- Currently stutters

Exclusion criteria: children who stutter

- Currently taking medication that affects brain function
- Major medical or psychiatric illness
- Language/motor delay

3.3. Speech, language, and behavioral testing

All participants will complete a hearing screening, oral mechanism exam, and a handedness assessment. Tests specific to adults vs. children are described below.

Adults. Stuttering severity will be assessed using the SSI-4, which consists of reading and conversation with a certified Speech-Language Pathologist (SLP). These samples will be video recorded for off-line transcription and quantification of stuttering behaviors.

Children. Standardized tests may include Clinical Evaluation of Language Fundamentals – 5th Edition [CELF-5], Goldman-Fristoe Test of Articulation- 2nd edition [GFTA-2], Bankson-Bernthal Test of

Phonology [BBTOP]) to determine whether the child has age-appropriate skills in speech and language. Stuttering severity will be assessed using the SSI-4 from a recorded speech sample that includes conversation during play with an SLP, and during narrative (story retell) using a wordless picture book (Frog, Where are You; Mayer, 1969). We may also administer the Test of Childhood Stuttering [TOCS].

Musical training. Because performance on rhythm-based tasks can be influenced by musical experience, we will collect information on number of years of formal and informal musical activities (individual/group lessons/ensemble participation, including what age they began) in children. Adults will complete the Goldsmiths Musical Sophistication Index test to assess present and past musical experience.

Working memory. To assess and control for working memory differences, adults will complete an automated operation span task. Children may also complete subtests from the Test of Auditory Processing Skills (TAPS-3) including forward/backward numbers and word memory. These tests are administered as part of ongoing studies in our lab.

3.4. Experimental design

Experimental tasks may occur over several visits. The primary experimental tasks (section 3.4.1) will be completed twice in adults and once in children. Adults will complete two study visits, while children are expected to require only one visit. However, in order not to overwhelm the child participants, depending on the participant, we may need to split up the study into 2 visits. The first visit will typically consist of consenting, standardized tests, and speech sample recording. If the family is willing, we will also complete the experimental tasks on this same visit, but some children may need 2 visits to complete the study protocol. Regardless of the number of visits for children, the tasks will be completed in the same order.

3.4.1 Rhythm tasks (primary experimental tasks)

Participants will complete tasks of rhythm perception and judgment that may include including finger tapping, speech synchronization, beat similarity judgments, and other similar tasks. These tasks will be completed on a computer or iPad and will take approximately 2 hours to complete. Participants will be seated in a comfortable chair in a quiet room during testing. Participants will wear headphones and a microphone to hear the stimuli and record any verbal response. These sessions may also be videotaped to code offline.

3.5. Data analysis

Primary Outcome Measure 1. Phase locking value (PLV) – Session 1 speech tasks.

The degree of synchronization will be measured by computing the PLV between subject's produced speech and the heard speech. The PLV is a vector with a value between 0 and 1 that reflects the phase difference between two signals.

Primary Outcome Measure 2. Phase locking value (PLV) – Session 2 speech tasks.

The degree of synchronization will be measured by computing the PLV between subject's produced speech and the heard speech. The PLV is a vector with a value between 0 and 1 that reflects the phase difference between two signals. Session 2 is for adults only.

Secondary Outcome Measure 1. Phase locking value (PLV) – Nonspeech tasks.

The degree of synchronization will be measured by computing the PLV between subject's produced nonspeech response and the auditorily presented stimuli. The PLV is a vector with a value between 0 and 1 that reflects the phase difference between two signals.

Covariates. We will explore effects of covariates, including stuttering severity, age, musical training, and working memory on task performance.

Statistical tests. Statistical tests will be chosen upon inspection of normality of the data, however it is like that Nonparametric Mann–Whitney–Wilcoxon and Wilcoxon signed-rank tests will be used for between- and within-group comparisons, respectively. We will control for multiple comparisons with FDR correction.

Sample Size and Power Analysis. Assaneo et al. (2019) reported moderate effect sizes for all comparisons that reliably separated participants into good and poor synchronizers. Importantly, these effects were stable across various sample sizes and time points. Using an effect size of .5, $\alpha=.05$, and power =.80, we expect to find significant differences with 50 AWS and 50 controls, for Aims 1 and 2 (independent samples t-test).

4. Protection of Human Subjects

4.1. Risks to Human Subjects

Human Subjects Involvement, Characteristics, and Design

Recruitment. The PI and Co-I Chang have established large recruitment databases for both adults (n~100) and children (n~250) who stutter and their fluent peers over the past decade, thus recruitment will primarily occur from within these pools and our ongoing studies. Additional recruitment will be achieved by reaching out to previous participants who meet the eligibility criteria, posting recruitment flyers in the area and posting on Reddit. Participants will be recruited through community advertisements such as in the hospital, community, local papers; word of mouth; letters to area clinicians; stuttering support groups; through the National Stuttering Association website; and on lab websites and Facebook pages <http://www.neurostutteringresearch.com>, <https://www.facebook.com/changstutterlab>, and/or Twitter @changstutterlab, @emilygphd, @sooeunchang

Adults. 50 AWS and 50 controls between the ages of 18-65 will participate in this study, though up to 500 subjects may be recruited/screened to account for disqualifications, attrition, etc. All participants must be primary speakers of American English. With the exception for stuttering diagnosis in the AWS group, inclusion will be restricted to those with no history of speech, language, hearing, reading, cognitive, psychiatric, or attention deficits. Additionally, AWS must currently stutter, with an overall Stuttering Severity Instrument 4 (SSI-4; Riley & Bakker, 2009) score of 10 (very mild) or greater, and/or at least 3% stuttering-like disfluencies (%SLD) and have had no speech therapy within the past year.

Children. 40 children (30 controls, 10 CWS) between the ages of 6 to 17 will participate in this study for the exploratory aim 3, though we may recruit up to 200 children to account for disqualifications, attrition, etc. Children will be excluded from participation if any of the following applies: Diagnosed/under treatment for any neurological or psychiatric conditions, head trauma with loss of consciousness, bilingualism, major medical illness, congenital abnormalities, hearing loss, language/motor delay (below -2SD on standardized assessments, see below), face, motor or reflex abnormalities. Additionally, CWS must currently stutter, with an overall SSI score of 6 (very mild) or greater, and/or at least 3% SLD measured during a speech sample (described below).

Study Procedures, Materials, and Potential Risks

Study procedures. Adult participants or parents and/or caregivers will complete forms and/or answer questions about their own or their child's behavioral, medical, social, and developmental states and speech, language and hearing background. In addition, all subjects will be audio-video recorded during all testing and experimental procedures. For children, at all visits, parents or guardians will be in the adjacent interview or observation room with all doors open or, if necessary, in the experimental testing room with the child if he/she is overly distressed at separation.

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) *Standardized test data*** (e.g., Clinical Evaluation of Language Fundamentals – 5th Edition [CELF-5], Goldman-Fristoe Test of Articulation- 2nd edition [GFTA-2], Bankson-Bernthal Test of Phonology [BBTOP], Nonword repetition task, the Stuttering Severity Instrument [SSI], Test of Auditory Processing Skills (TAPS-3)) as well as related hearing screening testing (e.g., pure-tone audiometry), **(3) *Audio-video recorded data*** (e.g., adult participants or children and their parents will be audio-videotaped in a laboratory setting to sample speech), 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 and/or during conversation).

Compensation. Adult participants and families of child participants will be paid \$50 for each visit.

Potential risks. Potential risks to participants are low and include the following: **(1) 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 members of the study team. Data will be managed using REDCap and Ripple. Any paper files will be placed in individual coded files that will be locked in a cabinet in the PI's office or lab. **(2) 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. They will also be reminded that participation is voluntary and that they have the option to skip questions or stop their participation at any time.

Modifications due to COVID-19. Behavioral measures listed above may be obtained via secure video connection (e.g., Zoom). Recordings of speech and language testing will be saved to appropriate cloud storage (MBox, or, soon, UM Dropbox) for sensitive data.

4.2. Adequacy of Protection Against Risks

Informed Consent and Assent

Consent to Participate: Adults. Written consent for participation will be obtained from the participant following an in person verbal overview of the study and consent form. Subjects will be informed that participation is voluntary and can be ended at any time with no penalty to them. The PI or trained study staff will obtain consent.

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 or the Speech-Language Pathologist. 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 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 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.

Assent to Participate: Children. Children age 8 and up will sign an assent form in the presence of the study team member under the same circumstances as described above for the parents. Children below the age of 8 will be read a child friendly assent script and verbally assent. 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.

Modifications due to COVID-19: We will use SignNow or REDCap to obtain e-consent. Study staff will schedule a secure video session (using Zoom with appropriate encryption options) to explain the study to

the family. Privacy (both of the researcher and the family) will be carefully ensured during explanation of study procedures as well as while answering any questions. The staff member obtaining consent will join the video call while being the only person in the room at their location. The participants will be instructed to join the video call in a private location as well.

Protections Against Risk

The study team has considerable experience in maintaining the confidentiality of participant data and has established procedures to ensure data confidentiality. First, every effort is made to ensure that all study data are always confidential, in terms of staff training and data storage, so that data cannot be linked to a particular person. Training of staff will include information about the importance of confidentiality and techniques to maintain confidentiality of all information reported by research participants. All investigators and research staff will be required to fulfill all training requirements for Good Clinical Practice (GCP) and for handling protected health information as outlined by the Health Insurance Portability and Accountability Act (HIPAA).

Data management will occur in REDCap and Ripple. Unique identification numbers will be assigned to all participants who complete the initial screening session. Only individuals working on the actual data collection with the need to have access will be able to see the identifiers. Consent forms will be maintained in REDCap or should in-person testing resume, may be stored separately from data in locked cabinets, because they contain identifying information/ participant ID. The identifiers will be maintained as long as data collection activities are ongoing, and up to 5 years following publication. Reporting of the research will involve aggregate data which will not permit identification of any individual patients.

To minimize risks we will, before each assessment begins (as explained above), thoroughly explain all procedures to all participants, including adults and 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.

At any time during any assessment, the adult participants, parents/guardians and/or children will have the opportunity to 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 with open doors throughout testing, or in the same room if the child has difficulty separating. Remuneration is important to encourage participation and study retention. Adults and families will be compensated for their participation, effort, time, and travel to assist them with costs and inconvenience to their schedules.

Data and Safety Monitoring Plan

The Principal Investigator, Dr. Garnett, will be responsible for monitoring the data safety and quality. Dr. Garnett will ensure that all relevant University of Michigan Medical School's Institutional Review Board (IRB MED) policies, procedures, and stipulations are being followed. Dr. Garnett will be responsible for reporting any amendments to the UM IRB MED prior to implementation of any changes to the protocol. Drs. Chang and Garnett will be responsible for providing training to all research staff. All of the

investigators and research staff involved in this trial will have completed the University of Michigan on-line educational programs on protection of human rights, Good Clinical Practice, and scientific ethics. Dr. Garnett will also be responsible for ensuring that other investigators and project staff adhere to the UM IRBMED policies.

Data will primarily be collected and maintained in REDCap and will include responses to questionnaires (intake screening form, developmental history, demographic information, behavioral questionnaires, therapy history, etc.), standardized test scores, digital audio recordings (subject responses during experiments), digital audio-video recordings (audio-video recordings of speech during the screening process), and coded behavioral data (e.g., behavioral observations and task performance measures coded by paper-and-pencil means and/or subsequently through the use of computer software). Physical forms that contain individually identifiable information (e.g., the signed consent forms) will be stored in a locked filing cabinet in a secured location that is accessible only to relevant study personnel. All other physical data forms (e.g., questionnaire responses) and all digital research material will be labeled only by a study code that reveals no individually identifiable information. These data will be accessible only to relevant study personnel. Any data stored on local computers will be de-identified. No identifying information will appear in any published reports resulting from this research without explicit approval from the identified subject and the IRB.

Ripple: Limited participant personal information will be kept in Ripple™, a secure web application designed for the storing and management of personally identifying information of research participants. Ripple was initially developed at the University of Michigan to provide a user-friendly, web-based secure interface where research teams can centralize the storage and management of research participants' personal information, including name, participant ID, demographics, and study workflow (e.g., appointments). Participant information managed with ripple is private and secure. This information is kept in fully encrypted format inside dedicated databases that are segregated from other Ripple accounts and thus only authorized study staff will have access to the study data. Likewise, Ripple infrastructure complies with the privacy and security guidelines of the Health Insurance Portability and Accountability Act (HIPAA), including 2048-bit data encryption in transit and at rest, automatic logoff, audit trail, daily backups in triplicate dedicated servers, firewall, custom access permission for lab members, zxcvbn password strength estimation, and enterprise administrative safeguards to prevent unauthorized staff from accessing participant information. Furthermore, Ripple is used only for storing personally identifiable information of participants and is not used to capture other research data (e.g., questionnaires, health records, etc.). This ensures that the personally identifiable information and research data are segregated.

The Data and Safety Monitoring Plan will be reviewed and approved by the Medical IRB at the University of Michigan. Monitoring and is intended to protect subjects' rights and safety, and to ensure the integrity and quality of the data collected. All of the investigators and research staff involved in this trial will have completed the University of Michigan on-line educational programs on protection of human rights, Good Clinical Practice, and scientific ethics. The study team will meet at least monthly to discuss study progress and any issues that may have come up. In addition, at monthly study team meetings, the following information will be reviewed.

- Informed consent obtained for each participant

- Adherence to protocol eligibility criteria
- Missing data, inconsistent data, or data outliers
- Check and review of all essential documents
- Review of all SAEs and subject withdrawals
- Enrollment issues and targets
- Protocol deviations and amendments
- Personnel changes and any required training
- Verifying continuous institutional review board (IRB) approval
- Any other issue as deemed important to the conduct of the study

Adverse events will be reported by Dr. Garnett. The timing of the reporting of an adverse event (unexpected events) to the UM IRBMED by Dr. Garnett will be done following the Standard IRBMED AE reporting timetable and according to relatedness, expectedness, and scale/severity. SAEs will be reported to the IRBMED per the UM IRBMED reporting guidelines and to the Project Officer for this grant. Dr. Garnett will be responsible for reporting adverse events. Notification to the NIDCD Program Officer of any expected *non-serious adverse events* and deviations from the protocol will be described in the annual progress reports. Unexpected adverse events that are not serious events will be reported to the NIDCD within 15 calendar days. *Serious adverse events* will be reported within 24 hours to the NIH by telephone or email, with a more detailed report submitted within 7 days to the NIH, IRB, and all participating investigators.