Title: Investigating the Effect of Stochastic Resonance Vibration on Gait and Balance and Upper Extremity Function in Children With Cerebral Palsy

NCT #: NCT04388787

Document date: 03/11/20

Document Type: Protocol and SAP

Investigating the effect of stochastic resonance on upper extremity function in children with cerebral palsy

SPECIFIC AIMS

Specific Aim: To determine effect of vibrotactile stochastic resonance (SR) on the speed and accuracy of manual reaching task in children with cerebral palsy.

Hypothesis: SR will improve manual dexterity and improve performance on standardized outcome measures of upper extremity function. No carry-over effects (i.e. continued improvements after device use) are expected.

BACKGROUND AND SIGNIFICANCE

Impaired integration of proprioceptive signals may contribute to deficits in motor planning and poor postural control and balance in individuals with developmental disorders including cerebral palsy (CP)[1]–[4]. Conceptualizing movement as a sensory-motor process we hypothesized that disordered proprioception and sensory integration contribute to atypical movement patterns in persons with CP.

Stochastic Resonance (SR) has been shown to enhance tactile sensory function[5], improve postural control[6] and enhance task performance in jumping activities[7]. In turn hypothesized that SR applied to extremities could facilitate functional movement in persons with CP.

The term stochastic is used because the frequency varies randomly from moment to moment but averages approximately 100 Hz. The term resonance is used because the vibration is created by the dampening of a sound wave within the actuators. This is essentially the same technology as is found in headphones. If you play music into your earphones and hold them in your fingertips you will feel the vibration. The 100Hz frequency is on the low end of the audible frequency range. When run at low amplitude it may be inaudible and undetectable to the touch sense. At higher amplitudes is felt as a light tingling vibration on the surface of the skin and makes a faint low pitched static noise. It is not painful and generally not bothersome.

In the therapy centers and rehabilitation clinics of the Children's Hospital of Richmond we have been using wearable wraps provided by Acclera^{inc} that deliver SR via a piezoelectric actuator, to explore whether SR could have utility in supporting gait and upper extremity function. In several subjects SR, applied to the wrist and shoulder, was found to improve the ability of children to reach more quickly and accurately for objects and manipulate them to perform a desired task.

In this proposal we plan to expand on our initial anecdotal observations of positive effect, in order to objectively quantify changes using validated measures of upper extremity function in children with CP treated with SR. We will use the box and blocks[8] and Shriners Upper Extremity Evaluation SHUEE [9]. Because CP encompasses a broad variety of movement impairments we will gather data on manual ability classification scale (MACS)[10]Test of Arm Selective Control and tactile sensory function to facilitate subgroup analysis [11].

RESEARCH DESIGN AND METHODS

A purposeful sample of 25 children with CP will be recruited to participate in the study. We will recruit children with no clinical complications that could interfere with their safe participation in all

the experimental study procedures. All subjects will be screened by a member of the study staff with a clinical background. Screening will include a standard clinical history and a physical exam.

Inclusion criteria

To be eligible to participate in the study, individuals will have to meet the following criteria:

- Diagnosed with cerebral palsy
- 3 years to 18 years of age
- Able to reliably express pain, discomfort or fear as reported by the parent/guardian
- Manual ability classification scale (MACS) levels I, II or III

Exclusion criteria:

Individuals will not be eligible to participate in the study if they exhibit any of the following:

- Any unstable medical condition. An unstable medical condition is a state of imminent threat to life such as shock, acute asthma, respiratory distress, severe infection and sepsis. Any patient in a clinic or therapy center presenting with signs and symptoms of an unstable medical condition will be directed to emergency medical services
- Any medical condition preventing active rehabilitation reported by the parent/guardian such as:
    - Thromboembolic disease, acute progressive neurological disorder, cardiovascular or pulmonary contraindications, aggressive behavior, severe cognitive deficits, joint instabilities and compromised bone health, recent or non-consolidated fractures, osteoporosis
- Subjects with cardiac pacemakers, electronic pumps or any other implanted medical devices
- Skin lesions affecting the areas where the device straps will be attached to the body

DESCRIPTION OF THE STUDY PROCEDURES

All study procedures will be carried out in rehabilitation clinics and participating therapy locations affiliated with Children's Hospital of Richmond (CHOR) at Virginia Commonwealth University (VCU).

RECRUITMENT PROCEDURES

All study procedures will be carried out in participating therapy locations affiliated with Children's Hospital of Richmond (CHOR) at Virginia Commonwealth University Health Systems (VCUHS) or at the physical medicine and rehabilitation clinics at the Children's Pavilion.

All subjects will be recruited by IRB approved study staff for this protocol. Assent will be obtained from subjects who are enrolled by proxy consent. Recruitment strategies will include the use of the following sources:

1. Attending physicians at CHOR-VCU may refer their patients with CP to the study. We will provide physicians with study information sheets and flyers.
2. Study divulgation through the CHoR Pavilion pediatric clinic services in and CHOR-VCU therapy centers.
3. Flyers posted in outpatient clinics, in pediatric neurosciences clinics and therapy. Study participants will receive up to $50 for completing the study. Additionally, for all subjects

driving to the CHOR-VCU, parking is free, and easily accessible at all of the study locations.

Recruitment will be ongoing for a 12-month period from the date that this protocol is accepted. Potential participants will be identified within the patient population presenting for care at clinics in the Children's Hospital of Richmond, Children's Pavilion and from patients receiving treatment at any of the six collaborating Children's Hospital of Richmond therapy centers which receive referrals from numerous external pediatric providers in the central Virginia area. Flyers will be posted in the Children's Hospital therapy centers and the children's pavilion, so that patients, physicians and therapist will be aware of the study.

Potential participants interested in the study may be screened enrolled directly by study staff members Jessica Lynn and Allison Wolf if they are present at the therapy location where a potential participant is identified, or will be able to request a screening through 1) Dr. Rolin's office phone number 804-310-2644 2)They can directly email Dr. Rolin to request a telephone screening.

Therapists at those locations will be briefed on the study and be able to refer appropriate participants to perform the study trials. If a potential study participant is receiving therapy services at a participating location, their diagnosis would be known to the referring therapist and determination of their manual ability classification is within the skill set of physical and occupational therapists. If present when a participant is identified Jessica Lynn (Bon Air therapy center) or Allison Wolf (Petersburg therapy center) will review the patient record to assure that the diagnosis of cerebral palsy has been stated in the clinical documentation by a qualified pediatric neurologist or physical medicine and rehabilitation specialist. They will then screen the patient to ensure they meet the eligibility criteria. If the diagnosis of cerebral palsy is not explicitly stated in clinical documentation but is suspected by the study therapist, Dr. Rolin will access the medical record and determine whether the diagnosis is accurate.

For participants that would be identified from the PM&R clinics, the process of screening fits into the normal flow of a clinic evaluation. When a patient presents to the PM&R clinic it is routine practice to establish the cause of a neurodevelopmental disability. The diagnosis of Cerebral Palsy is determined by the presence of abnormal tone and posture in an individual who sustained an injury to the developing brain in utero or up to three years of age. The cause of injury to the developing brain is confirmed in the interview with the family, and the review of for radiological and medical records. All persons with the diagnosis of Cerebral palsy ages 3 years to 18 years will be provided the opportunity to enroll in the study for aims. Assessment of test of selective arm control (TASC), modified ashworth scale (MAS), tactile sensory function and manual abilities classification scale (MACS) are part of standard clinical care.

For participants referred by non-rehabilitation physicians, Screening will be performed by and Dr. Rolin by phone. Dr. Rolin will confirm the potential patient's parents identity by requesting they provide their child's name and date of birth. Dr. Rolin will ask questions about the patient's medical history and physical developmental history in order to determine if the patient meets the eligibility criteria for the study. Review of their medical records will be necessary to confirm eligibility. Individuals will be informed that if deemed eligible, identifiable information (e.g. name, how to contact the subject, and his/her address) will be collected.

Participating locations include the following Children's Hospital of Richmond at VCU therapy centers:
Bon Air: 206 Twinridge Ln, Richmond, VA 23235
Petersburg: 321 B Poplar Dr #4, Petersburg, VA 23805
Children's Pavilion, 1000 E. Broad Street, Richmond VA, 22918

CONSENT PROCEDURES

When subjects first contact the study team, a member of the study team will provide them with a detailed description of the study over the phone or in person. If interested and deemed potentially eligible, a member of the study team will offer to provide the informed consent form to the subject. Subjects will be encouraged to call study staff with any questions or concerns that might have prior to their first study visit. Upon arrival a study site, prospective study volunteers and their parents/guardians will be given another copy of the informed consent form and study staff will review the procedures with them and answer any questions they might have.

When a patient presents for a scheduled study appointment, informed consent will be obtained by the Principal Investigator or a staff member designated by the Principal Investigator as adequately knowledgeable of the risks/benefits of the study and the vulnerability of the study population and capable to critically assess the subject's awareness of these factors. The subject will be encouraged to continue to ask questions and express concerns - if any - to study staff throughout their participation in the study. At this point, the study procedures will be described and the equipment that will be used during the study will be shown to the subjects and their parents/guardians. Study staff will explain all the study procedures and the risks associated with them as outlined in the informed consent form (ICF) and assent form. Enrollment will begin when the subject thoroughly understands and signs the informed consent form. Testing will only take place once the informed consent form is signed.

TESTING PROCEDURES

Subjects will be assessed in a single session in the participating therapy centers at the Children's Hospital of Richmond or at the Children's Pavilion. The visit will consist of the procedures described below and is expected to last 60-90 minutes.

If not completed in the past 6 months during a clinical visit, the following clinical assessments will be performed prior to initiation of study trials:

- Manual abilities classification score (MACS)
- Modified Ashworth Scale (MAS) to evaluate the severity of spasticity at the shoulder, elbow, wrist and fingers.
- Test of Arm Selective Control (TASC), focused on wrist and hand, to evaluate the severity of selective motor control impairment.
- Assessment of tactile and kinesthetic sensation impairments by monofilament and two point discrimination testing.

If the above listed clinical assessments were completed in the past 6 months, the data will be extracted from the participant's medical chart.

SR devices will be applied around the ventral and dorsal surface of the wrists as well as at the shoulder girdle on the tested (impaired) side.

Stochastic resonance (SR) wraps will be applied to the one or both wrists depending on whether the impairment is unilateral or bilateral. Two additional actuators will be secured around the shoulder. Stochastic Resonance refers to the vibration created by the device.
The threshold for detection of SR will be determined by the examiner prior to initiating the test condition. The intensity of the stimulation is adjustable with a scroll bar on the app and ranges from a 0 - 100. The examiner will gradually increase the stimulus intensity until the participant reports being able to feel it. The device will then be powered off. If for example the participant could feel the vibration at a level of 50 the device will be turned back on at 45 in order to provide stimulation at 90% of the detection threshold. Outcome measures will be assessed under the following conditions.

1) Treatment: SR applied sub threshold at 90% of detection threshold.
2) Sham: Patient wearing SR devices, but devices not turned on. Conditions 1&2 will be performed in random order, subject and examiner will be blinded to the condition.

3) Unblinded: SR is applied above threshold for detection at a patient selected intensity.

The following outcome measures will be assessed in each of the three different conditions described above. PDFs describing each test are attached separately.

1. Box and block test (B&B)[8]
2. Nine Hole Peg Test (9HPT)[12]
3. Shriners Upper Extremity Evaluation (SHUEE)[9]

During the visit, we will also collect video recordings while subjects perform the SHUEE. Video will be used for recording of the SHUEE and video recordings will be reviewed by an occupational therapy specialist blinded to the test conditions. It is worth emphasizing that, all subjects will be asked permission to be video recorded during the assessments as part of the consent process

There will be no local changes to the protocol's procedures. Participants younger than 6 years of age, and older participants with poor behavioral regulation may not be able to complete all of the clinical assessments and outcome measurements. Elements of the study protocol can be omitted if a child cannot or is reluctant to complete them. We anticipate that all patients recruited will be able to complete at minimum the MACS, Modified Ashworth Scale and two iterations of the box and blocks test. The minimum test elements would take less than 15 minutes to complete.

DATA ANALYSIS

Comparison of performance under the baseline, sham, treatment and unblinded condition for B&B, 9HPT and SHUEE will be determined by paired T test.

Subgroup analysis will be carried out by MACS level, TASC score and tactile sensory function.

The above-described descriptive statistics will inform the design of a future larger trial aimed to assess the suitability of SR as a rehabilitation tool and assistive device. Results will be utilized do determine effect size and conduct a power analysis to power further studies.

TREATMENT

There will be no treatment administered as part of this study. Hence, there are no alternative treatments to be considered.

RISKS

Every precaution will be taken to ensure the safety of study participants. Risks will be minimized by screening subjects to identify potential safety concerns. Trained study staff will closely observe/guard participants during all study activities. All the activities to be performed during the study are comparable to activities that are carried out during regular therapy sessions.

SAFETY

We do not anticipate any greater than minimal risk from participation. At the beginning of each study visit, subjects will be examined by trained study staff to ensure their safe participation in all study activities. Subjects will be guarded by trained study staff at all times during the study. Any medical issues or adverse events will be reported promptly to Dr. Rolin, who will arrange for any necessary treatment.

The clinical tests used in this study are standard instruments with minimal risks and will be administered by a study staff experienced in working with this patient population. Subjects will be asked to report all activity-related symptoms of pain or discomfort to the investigator, who will decide if medical care is warranted, and arrange for that care as appropriate.

All laboratory equipment meets hospital standards for electrical safety. The SR devices used in this study are powered by low voltage batteries and are completely isolated from other electrical sources such as power lines. The device produces vibration with the same technology that is present in commercially available headphones. They do not emit, heat, electrical current or substantial mechanical force that could cause injury.

If necessary, study staff will make accommodations such as using multiple sessions to collect data, using voice amplifiers for participants who have hearing loss or auditory sensory impairments and providing live examples of how to perform tasks to facilitate participation.

In the event of an AE or SAE, the study staff will remain in contact with the study participant until the problem has been resolved.

All video recordings will be stored in a secure study share drive that will only be accessible by study staff. Study staff will use the video to score subjects' SHUEE trials. Once the SHUEE exams have been scored the recordings will be destroyed.

FORESEABLE RISKS AND DISCOMFORT

When participating in the study, subjects will be at no greater risk of falls or injury than when seated in their home and community setting.

Subjects may become fatigued or uncomfortable during the visit. To minimize fatigue, subjects will be allowed to rest whenever they need to, and they will always be monitored by study staff during the study. Subjects may become frustrated if performing study tasks with their impaired extremity is too challenging. Elements of clinical assessments and outcome measures can be omitted if a child cannot or is unable to or reluctant to complete them.
Subjects may be uncomfortable due to the attachment of the SR device. If a child is made uncomfortable by the device, the study will be discontinued.

Unintentional loss/disclosure of Protected Health Information may occur and is considered a minimal risk due to the security measures enforced at Virginia Commonwealth University Hospital System (VCUHS). Confidential information will be kept in a locked filing cabinet and password-protected computers in the VCU-CHOR children's pavilion. The subject will be video recorded, which increases the risk of identification, though precautions will be taken to secure such data.

EXPECTED BENEFITS

We do not expect that subjects will benefit directly from participating in the study. Through their participation, participants may help in gathering knowledge suitable to develop future rehabilitation interventions based in the use of SR to approve functional movement. Thus, the study might benefit people with CP in the future.

EQUITABLE SELECTION OF SUBJECTS

Subjects recruited in the study will be representative of the target population (i.e. children ages 3-18 with cerebral palsy with gait or upper limb impairments). Due to the age of the study population, pregnant women are not likely to be eligible. No person will be excluded on the basis of gender, ethnicity, or race. Due to the relatively small budget of this pilot study, and because there is no expected direct benefit to the participants we will not include patients with limited English proficiency or wards of the state.

DATA AND SAFETY MONITORING

Because this study's procedures pose minimal risk to the subjects, bimonthly data and procedural reviews by the PI in consultation with study staff will be sufficient to identify and ameliorate any potential safety issues. Any safety concerns about the equipment or test protocol will be brought to the immediate attention of Dr. Rolin. Study staff will conduct bimonthly audits to ensure compliance with regulatory requirements for study documentation.

Approval of protocol, informed consent procedures, and recruitment will be obtained from the IRB during annual reviews.

Study staff will report any adverse events within 24 hours of its occurrence to the PI. Any serious adverse events will be reported immediately to Dr. Rolin. A written report will be submitted to the IRB within 48 hours. Remedial action to prevent reoccurrence of the event will be instituted prior to the resumption of study procedures.

MONITORING AND QUALITY ASSURANCE

Study staff will conduct bimonthly audits to ensure compliance with regulatory standards for study documentation.

PRIVACY AND CONFIDENTIALITY

The study will assign each new subject an alphanumeric identifier, which will henceforth be the sole means of identification connected to their data. All data will be collected under this identifier and will be kept isolated from any personal health information. All data will be stored locally on a

secure system. Information shared with individuals outside of Partners will be labeled using an alphanumeric identifier and will be devoid of personal health information.

Subjects' parents will be informed of their privacy rights and sign a HIPAA-compliant authorization form previously approved by the IRB.

Video recordings on secure VCUHS study sharedrive; only investigators listed on the study will have access to them. The video recordings will be destroyed after 7 years from the date of study closure in compliance with Partners Record Retention Policy. Patients will be given the choice to have video/photo material used for academic articles and presentations.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

No specimens will be collected during this study. No personally identifiable data will be sent to or viewed by individuals outside of Virginia Commonwealth University Health Systems (VCUHS). The study data will not be sold, and publicly available data will not contain any personally identifiable information. Subjects will be able to withdraw their data as outlined in Partners HIPAA authorization information material and in the informed consent form. Data will not be stored for future use not described in the protocol.

RECEIVING SPECIMENS

No specimens or data collected by researchers outside of Partners will be received.

References

[1] E. I. Blanche, S. Bodison, M. C. Chang, and G. Reinoso, “Development of the Comprehensive Observations of Proprioception (COP): Validity, Reliability, and Factor Analysis,” *Am. J. Occup. Ther.*, vol. 66, no. 6, pp. 691–698, Nov. 2012, doi: 10.5014/ajot.2012.003608.

[2] E. I. Blanche, G. Reinoso, M. C. Chang, and S. Bodison, “Proprioceptive Processing Difficulties Among Children With Autism Spectrum Disorders and Developmental Disabilities,” *Am. J. Occup. Ther. Off. Publ. Am. Occup. Ther. Assoc.*, vol. 66, no. 5, pp. 621–624, 2012, doi: 10.5014/ajot.2012.004234.

[3] J. Cooper, A. Majnemer, B. Rosenblatt, and R. Birnbaum, “The Determination of Sensory Deficits in Children With Hemiplegic Cerebral Palsy,” *J. Child Neurol.*, vol. 10, no. 4, pp. 300–309, Jul. 1995, doi: 10.1177/088307389501000412.

[4] D. J. Goble, E. A. Hurvitz, and S. H. Brown, “Deficits in the ability to use proprioceptive feedback in children with hemiplegic cerebral palsy:,” *Int. J. Rehabil. Res.*, vol. 32, no. 3, pp. 267–269, Sep. 2009, doi: 10.1097/MRR.0b013e32832a62d5.

[5] J. J. Collins, T. T. Imhoff, and P. Grigg, “Noise-enhanced tactile sensation,” *Nature*, vol. 383, no. 6603, pp. 770–770, Oct. 1996, doi: 10.1038/383770a0.

[6] L. A. Lipsitz, M. Lough, J. Niemi, T. Travison, H. Howlett, and B. Manor, “A shoe insole delivering subsensory vibratory noise improves balance and gait in healthy elderly people,” *Arch. Phys. Med. Rehabil.*, vol. 96, no. 3, pp. 432–439, Mar. 2015, doi: 10.1016/j.apmr.2014.10.004.

[7] D. L. Miranda *et al.*, “Sensory enhancing insoles improve athletic performance during a hexagonal agility task,” *J. Biomech.*, vol. 49, no. 7, pp. 1058–1063, 03 2016, doi: 10.1016/j.jbiomech.2016.02.022.

[8] M. Jongbloed-Pereboom, M. W. G. N. der Sanden, and B. Steenbergen, “Norm Scores of the Box and Block Test for Children Ages 3–10 Years,” *Am. J. Occup. Ther.*, vol. 67, no. 3, pp. 312–318, May 2013, doi: 10.5014/ajot.2013.006643.

[9] J. R. Davids, L. C. Peace, L. V. Wagner, M. A. Gidewall, D. W. Blackhurst, and W. M. Roberson, "Validation of the Shriners Hospital for Children Upper Extremity Evaluation (SHUEE) for Children with Hemiplegic Cerebral Palsy," *JBJS*, vol. 88, no. 2, pp. 326–333, Feb. 2006, doi: 10.2106/JBJS.E.00298.

[10] A.-C. Eliasson *et al.*, "The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability," *Dev. Med. Child Neurol.*, vol. 48, no. 7, pp. 549–554, Jul. 2006, doi: 10.1017/S0012162206001162.

[11] T. Sukal-Moulton, D. Gaebler-Spira, and K. J. Krosschell, "The validity and reliability of the Test of Arm Selective Control for children with cerebral palsy: a prospective cross-sectional study," *Dev. Med. Child Neurol.*, vol. 60, no. 4, pp. 374–381, 2018, doi: 10.1111/dmcn.13671.

[12] Feys Peters et al. The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. Mult Scler. 2017 Apr; 23(5): 711–720.