STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official title: The use of a program like The Listening Program® with bone conduction headphones changes hypersensitivity to sound and behavioral responses associated with flight/fight responses of children with Autism Spectrum Disorder (ASD) therefore increasing adaptive life skills.

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Title of the Protocol:

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Principal Investigator: Suzanne Vercontaire, OTR/L
Co-Investigator: Caitlin Deville, PT, MPT, DSc
Co-Investigator: Kassie Missell, OTR/L, OTD

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Children's Health
1935 Medical District Drive
Dallas, TX 75235

Study Protocol

I. Introduction and Purpose

Per data collected by the Center for Disease Control and Prevention's (CDC) Autism and Developmental Disabilities Monitoring Network, the prevalence of Autism Spectrum Disorder (ASD) is increasing - in the year 2000, 1 in 150 children had a diagnosis of ASD In 2016, approximately 1 in 54 children has been identified with (ASD) according to estimates from CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network. Notably, ASD is 4.3 times more common in boys (CDC, 2020).

In 2013, the "Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5" published by the American Psychiatric Association changed the diagnostic criteria for ASD (American Psychiatric Association, 2013). One of the changes included the addition of hyper- or hypo reactivity to sensory input. For example, adverse response to specific sounds. Indeed, sensory-perceptual abnormalities are seen in approximately 90% of individuals with ASD (Gomez et al., 2008).

The most common sensory perceptual abnormality is auditory sensory over-responsivity (SOR) SOR is characterized by a quicker, more intense, and/or longer duration response to sensation than those with typical sensory responsivity (Miller et al., 2007. Children with ASD can have abnormal and often severe behavioral reactions to a variety of sounds in their everyday environment (Doman & Lucker, 2015). The fight or flight response elicited by auditory SOR increases maladaptive behavioral responses in a variety of environments and negatively impacting adaptive living skills. Adaptive life skills are everyday skills needed to function and meet the demands of one's environment, including independent self-care and social interaction.

Given the increased prevalence of ASD and the heightened awareness of sensory over- and under-responsivity (SOR) (SUR), particularly to auditory input, as a component of ASD, there is a growing need for evidence-based treatments to relieve discomfort and lessen behavioral reactions to a variety of every day environmental sounds to support improved adaptive life skills.

The objective of this study is to investigate changes in adaptive life skills and behavioral responses in children with ASD using Advanced Brain Technology's Listening Program ® Spectrum music utilizing Waves ™ (bone conduction) headphones.

The information obtained will contribute to a more comprehensive and evidence- based approach to the treatment of auditory SOR in children with ASD. It is expected that reducing auditory SOR will improve adaptive living skills at home, school, and in the community.

2. Background

There are limited approaches to specifically address auditory SOR in children with ASD. Exposure therapy (or systematic desensitization) may be a treatment option; researchers are investigating this approach. Many children receive sensory integration therapy, but this approach does not specifically target auditory SOR. Some families are advised to have their children avoid noxious stimuli or use compensatory techniques such as wearing headphones or ear plugs. While preliminary research suggests that use of noise attenuating headphones may reduce sympathetic activation for children with ASD and auditory SOR, this approach does not seek to change or alter the underlying cause of sympathetic activation (Pfeiffer et al., 2019). In addition, there is some concern that avoidance of sounds using ear plugs, noise canceling, or noise attenuating headphone can lead to increased anxiety and exacerbate the negative effects of hyperacusis (Juris et al., 2014).

Sound-based interventions are promising options to treat hyperacusis and subsequent auditory SOR in children with ASD. Over the years a variety of sound-based interventions, including music-based auditory stimulation and listening therapies, have been designed to reduce sound sensitivities including Tomatis-the Mozart Effect developed in the mid-20th century (Thompson & Andrews, 2000). According to Berard (1993), listening-based intervention that involved electronic modified music reduced maladaptive auditory processing and improved aspects of behaviors and learning. In 1997, the company Vital Links developed *Therapeutic Listening* and proposed the theory of relationship between sensory processing, brain and behavior. In 1998, the company Advanced Brain Technologies developed The Listening Program® and created Spectrum music in 2012 to improve auditory processing and reduce auditory sensory sensitivities. The company Integrated Listening Systems (ILS), founded in 2007, developed Safe and Sound protocol to reduce auditory sensitives.

Initial studies provide some support for sound-based interventions for children with ASD and auditory SOR. In 2014, Gee et al. conducted a case study to investigate changes in sensory processing, SOR, and auditory SOR-related behaviors for a 7 year-old child with ASD and auditory SOR after using The Listening Program® for 10 weeks. They noted a decrease in the number of negative and self-stimulatory behaviors during the study, but it was unclear if these

changes were due to The Listening Program® or the potential therapeutic effect of repeated exposure to one of the outcome measures – the Sensory Over-Responsivity Scales. Gee et al. (2015) used an ABAB design to study the effects of 10 weeks of The Listening Program® on three children with ASD and auditory SOR. There was a high variability of responses, but each child demonstrated an improved behavioral response during at least one phase of the study. Schoen et al. (2015) conducted a pilot study to explore the effects of Integrated Listening Systems Focus Series – another type of sound-based intervention – on seven children with sensory processing impairments after 8 weeks of intervention. They used a nonconcurrent AB design with a postintervention no treatment phase, and participants showed improvement in home and education related goals. Most participants also demonstrated changes in arousal level, as measured by parent report and the Sensory Challenge Protocol.

Our study will investigate the effects of a sound-based intervention developed in 2012 to specifically address the needs of children with ASD and children with hyperacusis and/or auditory SOR - The Listening Program® Spectrum music utilizing Waves™ (bone conduction) headphones by Advanced Brain Technologies. This program emphasizes low frequency music over an extended period of time; the duration recommended by Advanced Brain Technologies is 40 weeks. To our knowledge, this will be the first study investigating the effects of this specific program as well as the first study investigating the use of a sound-based intervention for 40 weeks for children with ASD and auditory SOR.

According to Advanced Brain Technology, The Listening Program ® Spectrum music requires a person listen to psycho-acoustically modified classical music online using specialized “Waves” ™ headphones. The headphones transmit sound through bone conduction which provides another mode of perceiving sound (https://advancedbrain.com). The Listening Program ® can be carried out in the home environment with either the base schedule, two fifteen minute sessions at least 30 minutes apart, or a condensed schedule for 30 minutes.

The use of bone conduction was originally used for differential diagnosis between conductive and sensorineural hearing loss by using vibration on the mastoid bone to improve perception of sound (Allen, 2008). This technology started in the 19th century with the usage of the tuning fork and evolved to the bone conduction transducer during the 20th century (Stefan, Stenfelt, 2011). In the 1960’s, Dr. Alfred Tomatis created a method using bone conduction along with classical music to influence the vestibular system as well as the subcortical and cortical levels of the brain to deepen somatosensory awareness (Allen, 2008).

Bone conduction allows the listening experience to go deeper into the vestibular system which is purported to reduce stress, help regulate the “fight or flight” response, and allow the listener to achieve a state of calm and relaxed alertness. This theory is based on the function of the vagus nerve, the 10th cranial nerve, which has branches that extend to the eardrum. Stimulation of the vagus nerve stimulates the parasympathetic nervous system (Allen, 2008).

3. Concise Summary of Project:

Children with a diagnosis of ASD with auditory SOR to sound, ages 5 to 10 years, will be recruited from the campuses of Children's Health Rehabilitation and Therapy Services and the Center for Autism and Developmental Delays (CADD Clinic).

The study will use a nonconcurrent AB multiple baseline design, with A representing the baseline phase and B representing the intervention phase with a postintervention non-treatment phase. At baseline (A), demographic information will be collected and the following outcome measures will be completed: the Pediatric Evaluation of Disability Inventory Computer Adaptive Test with ASD Scales (PEDI CAT(ASD), Sensory Processing Measure(SPM) home form, the Adaptive Behavioral Assessment System 3rd Edition ABAS-3 and Autism Treatment Evaluation Checklist (ATEC). During the intervention (B) phase, parents of participants in the treatment group will be educated by the investigators on use of The Listening Program at home, and then participants in this group will receive treatment at home utilizing The Listening Program for 40 weeks. Testing, using the same 4 outcome measures, will be completed at the 41st week after use, and then again after 3 months of no treatment. Between testing sessions, caregivers and investigators will set up three phone or hospital-approved virtual platform meetings at approximately 10 week intervals to check in and answer questions. The study is expected to run until the target number of 5 to 8 participants are enrolled.

4. Study Procedures:

Methodology: The caregivers of the children will meet with the principal or co-investigator for a 90-minute to 2-hour meeting. The meeting will include education on auditory SOR and the usage of the listening program and utilization of the wave bone conduction headphones for. All caregiver questions will be answered with caregivers verbalizing understanding of the research process, auditory SOR and equipment use. During this initial session, 4questionnaire-based assessments, demographic information sheet and Consent to Participate in Research Form will be completed. A handout will be provided to the parent or caregiver which will include proper care, use and return of the "Waves" ™ headphones and amplifier along with instructions to utilize the online listening system. Parents and caregivers will have the opportunity to ask questions and receive clarification about the study prior to signing the consent form.

The questionnaires based assessments include:

1. Adaptive Behavior Assessment System, Third Edition (ABAS-3)

Patti Harrison, PhD, Thomas Oakland, PhD

The third edition of this highly regarded assessment gives a complete picture of adaptive skills across the life span. Per the test manual, the ABAS-3 has good test-retest reliability (*r* .72 - .84 across all areas/domains). The ABAS-3 is easy to administer and score. It is particularly useful for evaluating those with developmental delays, autism spectrum disorder, intellectual disability, learning disabilities, neuropsychological disorders, and sensory or physical impairments (Harrison & Oakland, 2015). The ABAS-3 covers individuals from birth to 89 years of age (www.wpspublish.com/).

2. PEDI-CAT (ASD)

Stephen M. Haley PhD, PT, FAPTA Wendy J. Coster PhD, OTR/L, FAOTA Helene M. Dumas PT, MS Maria A. Fragala-Pinkham PT, DPT, MS Richard Moed MPA

The PEDI-CAT (ASD) is a module of the PEDI-CAT that has been validated for the population of children and adolescents with ASD. Research also supports the test-retest reliability of the PEDI-CAT (ASD) with ICC values indicated excellent score reliability over the test–retest period for all PEDI-CAT (ASD) domains: The Daily Activities ICC value was 0.92, the Social/Cognitive value was 0.86, and the Responsibility value was 0.90. This module includes additional directions to help parents select an appropriate rating given the unique characteristics of children with autism. In addition, the scores in the Social/Cognitive domain are based on the unique patterns of children and youth with autism, but are expressed on the same metric as the original PEDI-CAT (Kramer, Liljenquist & Coster 2016) The PEDI-CAT is designed for use with children and youth (birth through 20 years of age) with a variety of physical and/or behavioral conditions (https://www.pedicat.com/).

3. Sensory Processing Measure™ (SPM™)

L. Diane Parham, PhD, OTR/L, FAOTA, Cheryl Ecker, MA, OTR/L, Diana A.Henry, M.S., OTR/L, FAOTA, et al

The *Sensory Processing Measure* (SPM) is a norm-referenced assessment of sensory integration/sensory processing that gathers information about a child's behavior, coordination, and participation at home, in the community, and/or at school. For the purposes of the study the Home Form will be utilized. Per test manual, the SPM has good test-retest reliability ($r \geq .94$ on all scales). Separate scores are provided for social participation, five sensory systems, and motor planning in the home. Additional scores may be obtained for six different school settings, including art class, music class, physical education class, the playground, the cafeteria, and the school bus. *Sensory Processing Measure* (SPM) can be used with 5- to 12-year-old children, including 5-year-olds who have already started kindergarten (Parkham, Kuhaneck, Henry & Glennon, 2007).

4. Autism Treatment Evaluation Checklist (ATEC)

Bernard Rimland, PhD, Stephen M. Edelson, PhD

The ATEC is a 77-item assessment tool developed at the Autism Research Institute. It was developed to provide a free, easily accessible, and valid tool to measure changes in ASD symptoms over time. The ATEC can be completed by parents, teachers, or others who see the individual's behavior on a regular basis. The ATEC consists of four subtest scales: Speech/Language/Communication, Sociability, Sensory/Cognitive Awareness, and Health/Physical Behavior. The four subscale scores are used to calculate a total score (77 items – score range 0 to 180). A lower score indicates less severe symptoms of ASD and a higher score correlates with more severe symptoms of ASD. Baseline

scores can be compared with post-intervention scores to assist with determining intervention efficacy. Per data collected by the Autism Research Institute, Pearson split-half coefficients were calculated to examine the internal consistency. Subscale coefficients ranged from .82 - .92 and the total score coefficient was .94, indicating high internal consistency (Rimland & Edelson, 1999). Research shows the ATEC is highly correlated (ρ = .71, p < .0001) with the Childhood Autism Rating Scale (CARS), which is a widely used and well validated measure used to identify ASD (Geier et al., 2013), and there is some preliminary evidence that supports the use of the ATEC to monitor progress of children with ASD over time (Magiati et al., 2011).

The caregivers will be given a choice between a base schedule which includes two 15 minute sessions with at least 30 minutes in between sessions of listening per day for 5 consecutive days and two days off or a condensed schedule of one 30-minute session of listening per day for 5 consecutive days and two days off. A handout for the selected listening schedule will be given during the initial session.

Testing – using the same 4 questionnaire based assessments- will be completed at the 41st week after treatment these assessments, and then again after 3 months of no treatment. These visits are expected to take approximately 60 – 90 minutes, and the final visit may be completed in-person or using a hospital approved virtual platform.Between testing sessions for both groups, caregivers and investigators will set up three phone calls or hospital approved virtual platform meetings at approximately 10 week intervals to check in and answer questions.

The total time spent face-to-face with a study investigator is expected to be about 2.5-5 hours per participant.

5. Sub-Study Procedures:

This project does not have a sub-study.

6. Criteria for Inclusion of Subjects:

Children will be eligible to participate in this study if they are:

Between the ages of 5 and 10 years old
Diagnosis of autism spectrum disorder
Auditory SOR defined by “Some Problems or Definite Dysfunction” on the Hearing section on the Sensory Processing Measure Home Form.
Caregiver must be available to supervise listening sessions at home
English Speaking

7. Criteria for Exclusion of Subjects:

Children will be excluded from the study if they are:

Diagnosed with seizure disorder
Hearing impairments
Cerebral palsy
Fragile X syndrome or genetic disease
Previous use of a listening based system
Non-English speakers

8. Sources of Research Material:

All the data described here is being collected specifically for research purposes.

Parents/legal guardians of the study participants will provide general information about their child by completing a demographic form. Information requested will include: the child's full legal name, age, gender, co-morbidities, list of medications being taken, physician's name, list of previous and current therapies and contact information prior to use of the listening-based program. The research data collected from the assessments Adaptive Behavioral Assessment Systems (ABAS-3), Pediatric Evaluation of Disability Inventory (PEDI-CAT-ASD) and the Sensory Processing Measure (SPM), and the Autism Treatment Evaluation Checklist (ATEC) will be the source of research data being collected.

9. Recruitment Methods and Consenting Process:

Potential participants will be given flyers that will be provided by rehabilitation services at Children's Health Rehabilitation Services at all locations either by a therapist or by the front desk. At the Center for Autism and Developmental Delays (CADD) clinic by flyers will be available in lobby area and/or physicians will give flyer to individual patients. They can contact the researchers via phone or email after learning of the study. If a therapist who is not a member of the study identifies a potential participant and learns of the parent's interest in the study, the therapist may inform the study team who would then contact the parent to discuss participation in the study. The research team would contact the parent only if the therapist indicates that the parent is agreeable to being contacted by the researchers. If there is a lack of potential participants after three months, flyers will be distributed outside of the Children's Health System. With administrative permission flyers to be given to local pediatricians' offices, private schools for children with special needs, and pediatric therapy private practices. The researchers will also register the study in ClinicalTrials.gov.

Interested subjects can contact the research team via phone or email or vice versa so the team can answer any questions parents may have regarding the study. If they are interested in moving forward after that, a member of the research team and the parent will speak on the phone to complete an eligibility screening, including 8 questions on auditory SOR (Hearing Section) on the Sensory Processing Measure- Home Form to determine if the child meets the criteria for auditory SOR for this study. On the Sensory Processing Measure (SPM), the Hearing section score must indicate "Some Problems" or "Definite Dysfunction" to be enrolled in this study. After parents have their questions answered they will be asked whether they are

interested in having their child enrolled in the study.. If the child is eligible and the if the parents agree to have their child participate, a meeting at a Children's Health Specialty Center will be set. During this meeting, the study principal or co-investigator will complete the consent interview with the family. If the family agrees to participate after completing the consent interview and signs the informed consent form, the meeting will continue and the initial visit will begin.

10. Potential Risks:

This study poses no more than minimal risk to participants and their families. The questionnaire-based assessments used in the three data collection sessions are often administered by occupational therapists in pediatric rehabilitation settings, among other places, and are not known to cause any harm. Any adverse physical or psychological harm to study participants during the administration of Listening Program® Spectrum music with Waves ™ (bone conduction) headphones is unlikely. The parent will have instructions on safe and appropriate usage of the Listening Program® at home, including recommendation to supervise their child during usageand parents be in the line of sight of their child, how to don the headphones correctly (correct ear placement will be noted on the headphones), and how to accommodate fit of headphones for small children (e.g., using a headband or rolled up bandana to keep them in place). However, if the child is unattended while doing the Listening Program, possible risks include: chewing or otherwise tampering with the cord, moving the plug from the correct placement in the amplifier, raising the volume to an uncomfortable level, or discomfort due to headphones slipping out of place or placed backwards on the child's head. There may also be the risk of strangulation from the cord if the child is left unsupervised.

11. Subject Safety and Data Monitoring

During the three data collection sessions study participants will be asked to come to a Children's Health Specialty Center to fill out the 4 questionnaire-based assessments with the principal investigator or co-investigator. If preferred, parents can complete the final data collection session using a hospital approved virtual platform.

Given the nature of this study a Data Safety Monitoring Plan is not needed.

12. Procedures to Maintain Confidentiality:

Study participants have been assigned a code that has been used on all data collection forms. The code will be known by the PI and co-investigators. The de-identified test forms (data collection forms), research binder and demographic page will be stored electronically in a password protected drive. Paper copies of consent forms will be kept in a locked file cabinet in the Rehabilitation Services office at Children's Health Richardson Specialty Center. The information collected by the investigator and co-investigators will be retained by Children's Health for 10 years after completion of the study according to the data retention policy for research. De-identified data including demographics and results of questionnaires (or any other data) will be shared with Advanced Brain Technologies.

We do not intend to apply to NIMH for a Certificate of Confidentiality.

13. Potential Benefits:

The findings from this study will begin to fill in a gap of knowledge regarding the utilization of listening-based programs for the treatment of auditory (SOR) in children with autism. This study will also serve as a catalyst for other studies investigating the potential benefits of listening based programs.

The parents, legal guardians, and children who participate in the study will be provided with an oral report using lay terminology that summarizes changes in the questionnaires following the study, which they may consider a potential benefit to participation in the study. The patients will be provided with listening-based therapy at no cost. Aside from this there is no other direct benefit to participants.

14. Biostatistics:

Sample Size and Power: This is a pilot study. Each patient is measured at 3 phases: baseline, intervention and post intervention. The total sample size is of 8 patients. This sample size is similar to the sample of 7 patients in the pilot study reported by Sarah A. Schoen, PhD, OTR, Lucy J. Miller, PhD, OTR, and Jillian Sullivan, PhD, 2015.

Statistical Analysis Plan: Descriptive analyses will be performed for the demographic and prognostic characteristics of the patients. Categorical variables will be reported with frequencies and proportions; continuous variables will be reported with means and standard deviations. The primary outcome is the ABAS-3 general adaptive composite score. The raw scores will be summarized in a box-and-whisker plot illustrating score distributions at baseline, at intervention and post intervention. Shapiro-Wilk and Kolmogorov Smirnov tests will be used to test whether the composite score follows normal distribution. If the composite score deviates significantly from normal distribution, transformation will be applied. Piecewise linear mixed-effects model could be used to model the score change over the 3 stages in the study. The statistical analyses will be performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC).

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