

**Developmental Pilot Study of External Trigeminal Nerve
Stimulation for ADHD**

NIMH R34 MH101282

James J. McGough, M.D., M.S. and Sandra K. Loo, Ph.D.

(Principal Investigators)

Clinical Trials Registration: NCT02155608

**Informed Consent Document
04/28-2015**

UNIVERSITY OF CALIFORNIA, LOS ANGELES

PARENT PERMISSION TO PARTICIPATE IN RESEARCH

Developmental Pilot Study of External Trigeminal Nerve Stimulation (TNS) for ADHD

“TNS & ADHD”

INTRODUCTION

James McGough, M.D., Sandra Loo, Ph.D. and associates from the Department of Psychiatry & Biobehavioral Sciences in the David Geffen School of Medicine at the University of California, Los Angeles, are conducting a research study. This study is being paid for by a grant from the National Institute of Mental Health. Some equipment and study supplies are provided by NeuroSigma, Inc., the company that manufactures the TNS device. NeuroSigma has no involvement in the design or conduct of this study.

The researchers will explain this study to you. **Research studies are voluntary and include only people who choose to take part.** Please take your time about deciding whether to participate in this study. Before deciding:

- You can discuss this study with friends and family.
- You can also discuss it with your health care doctor or request a second opinion.
- If you have any questions, you can ask the researchers for more information before deciding to participate.

The research team is asking your child to be in this study because he or she has difficulties due to symptoms of inattention, hyperactivity, and/or impulsivity. Your child might also have been previously diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) or you think your child might have ADHD.

WHY IS THIS STUDY BEING DONE?

This study will test if a non-medication treatment called Trigeminal Nerve Stimulation (or TNS) is helpful for children with attention-deficit/hyperactivity disorder and a range of other problems related to memory, concentration, sleep, and mood. The study will also assess how long it takes TNS to work, how long benefits last after treatment stops, and ways in which TNS improves brain activity. If this study is successful, it could lead to establishing TNS as a non-medication treatment for ADHD.

The device used in this study is known as the NeuroSigma Monarch eTNS™ System. It is a non-invasive medical device that stimulates the trigeminal nerve using an external electric conductive patch, which resembles a Band-Aid, directly on the forehead. **TNS is not an approved treatment for ADHD.** TNS is approved in Europe to treat some types of depression. Several studies in the United States also suggest that it might be useful for depression, anxiety, and seizure disorders. One small study at UCLA showed

that TNS is associated with improved parent ratings of ADHD symptoms, as well as improvements in concentration, mood, and sleep. This study builds on the previous UCLA ADHD study will provide information that will help plan future larger studies. TNS is approved in the United States by the FDA for research use.

WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

The study will last approximately 6 weeks. After evaluation and meeting entry requirements, you and your child will be instructed on applying the device to administer TNS. Treatment will be given every night during sleep for 4 weeks. You and your child will return to clinic once each week during this period to assess response. After 4 weeks, TNS treatment will end. You and your child will return to clinic one week after treatment ends to assess how long treatment effects persist.

You will not receive a full explanation about some of the tests in this study until after your child has completed them. These are minimal risk procedures that are not explained fully to help with the scientific process. You and your child will be fully debriefed about these tests after they are finished.

Evaluation Visit

The Evaluation Visit will take 2 to 3 hours. During the evaluation we will ask you and your child a lot of questions about your child's behavior and ask you and your child to complete numerous questionnaires and rating scales. We will measure your child's height and weight, pulse, and blood pressure. We will also give your child some tests to see if he or she has learning problems. We will ask your child to give us some saliva by spitting into a test tube. The saliva will be used to look at your DNA to see if your child's genes influence behavior. We will also give you a short rating form to give to your teacher, and ask that you bring this back at your next visit. We usually complete this evaluation in one day, but will break it up over several days if that is more convenient for your family. Children who are currently well controlled with ADHD medication or have an immediate need to begin taking ADHE medication will not be eligible for this study.

Baseline Visit

If during the evaluation we find that your child meets study requirements, you will be invited to return for a Baseline Visit. The Baseline Visit should take 1-2 hours. During this visit, we will again measure your child's height, weight, pulse, and blood pressure. We will ask you to complete some questionnaires and rating scales, and the doctor will ask you some questions about your child's behavior. We will obtain an EEG, a 30-45 minute exam that uses a cap with electrodes worn on the head to assess brain activity, to measures your child's brainwaves while taking some tests on a computer.

Participants in the study will be randomized to one of two groups. In one group, the "active group", your child will receive brain stimulation that we believe will be medically effective for ADHD. In the other group, the "sham group", the device will not deliver active stimulation to your child's brain and we believe this will have no effect on ADHD

symptoms. Your child will be assigned randomly to one group or the other in a manner similar to flipping a coin. **There is an equal chance that your child will be in the active or sham group.** Only one member of the study team will know which group your child is in. This is what we mean by a double-blind study in which neither you nor the research staff will know which group your child is in until the end of the study.

Staff will instruct you on how to use the device. The device is similar in size to an iPod that you can clip to your child's t-shirt or pajamas. Small wires from the unit connect to strips that are a lot like Band-Aids and which are placed on your child's forehead. We will give you a chance to practice putting this on and turning on the machine. Study staff will gradually adjust the stimulation strength. The most common sensation may be pressure or tingling in or near the eyebrows, but some people do not feel anything. If your child does feel something, he or she will be asked to describe and rate its intensity. If it is uncomfortable, the stimulation strength will be immediately decreased. It is not uncommon that your child might not feel anything during stimulation. Lack of sensation with the device does not mean it is not working.

Your child will need to use TNS for about 7 to 9 hours each night. You should place and turn on the device 8 to 9 hours before your child's usual morning wakeup time. Most of the TNS will occur during sleep. Each morning you can throw away the connection strips. You will use new ones each night. You will need to change the unit's battery every other night.

At each visit, we will give you sufficient strips and batteries for the next week. You need to bring the stimulator as well as any unused strips and batteries when you return for each weekly visit

It is important that you keep the stimulator safely away from others, such as other children in the family. Do not share your device with others.

There are some precautions your child should follow while wearing the device. Always place the strips over the forehead, directly above the eyebrows, as directed by the study staff. Never place the electrodes on the chest, neck, or other body parts. Never place the electrodes over broken skin. Always turn the device off before removing the strips. Your child should not take a shower or bath or go swimming while wearing the device. Neither you, your child, nor anyone else should make any adjustments to the stimulator on your own.

Treatment Visits 1-3

These weekly visits should require approximately 1 hour of time. We will measure your child's height, weight, pulse, and blood pressure. We will ask you and your child to complete some rating forms. The study doctor will ask you questions about your child's behavior. Your child will complete some simple tests. We will ask you to have your child's teacher fill out a brief rating form about how your child has been doing.

If you have access to the Internet and if you prefer, you will have an option to complete Visit 2 and 3 ratings without coming to UCLA. If you choose to do this, the study investigator will also contact you by phone to obtain additional ratings and assess your child's health and safety. If you complete the ratings within the required window, you will still receive \$10 for each visit when you return to UCLA for Visit 4.

Treatment Visit 4

This visit will require approximately 2 hours of time. We will measure your child's height, weight, pulse, and blood pressure. We will ask you and your child to complete some rating forms. The study doctor will ask you questions about your child's behavior. We will ask you to have your child's teacher fill out a brief rating form about how your child has been doing.

At this visit, we will obtain a second EEG. During the EEG, your child will complete some simple tests. Your child will also be asked to play an additional computer game during the EEG that will provide a chance to earn up to \$25 in prize money.

TNS treatment will end after this visit. You will be asked to return the stimulator device along with any left over batteries and conduction strips.

Visit 5

This visit should require approximately 1 hour of time. We will measure your child's height, weight, pulse, and blood pressure. We will ask you and your child to complete some rating forms. The study doctor will ask you questions about your child's behavior. Your child will complete some simple tests. We will ask you to have your child's teacher fill out a brief rating form about how your child has been doing.

At the end of this visit, the study doctor will tell you if your child received the active or sham TNS treatment.

At the end of this visit, the study doctor will find out which treatment group your child was assigned to and will give you that information.

Children assigned to the sham condition will be offered the opportunity to remain in the study for an additional 4 weeks and to receive active TNS treatment during that time. A stimulator and supplies will be returned to you and your child will be able to resume nightly treatment. You will be asked to return to the clinic at the end of two and four weeks of treatment so that response can be assessed. You will be asked to complete rating scales and the study physician will ask questions about your child's progress. Treatment will end after 4 weeks and you will be asked to return the device and any remaining supplies.

Children assigned to the active group or those in the sham group who are not interested in obtaining active treatment will end study participation at Visit 5.

One-Year Extension

Children who improve sufficiently after active TNS treatment in the initial clinical trial will be eligible for one year ongoing TNS treatment at no additional cost. If you choose to participate in this one year extension, you will be asked to return to UCLA for follow up appointments every 3 months. During these visits, we will assess your child's ongoing ADHD response, safety, and compliance with similar measures that are used in the double blind trial. At each of these visits, study staff will also insure that the device continues to work properly and will provide you with an additional 3 months of TNS supplies.

If the device breaks, we ask that you return it as soon as possible so that it can be replaced. You will have no financial responsibility for the device if it becomes damaged or lost, although we do ask that you do your best to care for it.

You are free to discontinue participation in the one-year extension at any time. If you choose to discontinue TNS, we ask that you come to UCLA for a final termination visit and that you return the device and any remaining supplies.

HOW LONG WILL I BE IN THIS STUDY?

The initial clinical study will last approximately 6 weeks. There is an option for an additional 4 weeks of active treatment for those randomized to the sham group. If your child has sufficient improvement with active TNS treatment, you will have an option to receive TNS treatment for an additional year without and cost to you. At the end of the study, you will be referred if you wish to the UCLA ADHD Clinic or another provider where your child can get standard ADHD treatment.

WHAT KINDS OF RISKS OR DISCOMFORTS CAN I EXPECT?

Known risks and discomforts:

Risks of TNS: The device is safe and designated by the U.S. FDA as a "non-significant risk device." The risks of using it are similar to the risks you experience in everyday life. Your child might experience some discomfort on the forehead during the initial visit while staff adjusts the level of stimulation. Some patients experienced tingling or pressure in the scalp or teeth, headaches, and eye blinking. If your child has these problems, notify staff right away and we will adjust the device to eliminate them. Some patients who have worn the strips longer than we are asking in this study developed skin rashes under the site where the strips were applied. When it has occurred, these rashes have gone away with decreased wear times and cortisone cream.

Risks of Assessment Procedures: There is a chance you or your might get upset during clinic visits due to 1) embarrassment or anxiety when asked to discuss personal medical

history, 2) anxiety about performance during testing, or 3) fatigue or boredom during tests.

Risks of Behavioral Worsening: It is not known if TNS will have any effect on ADHD. Both the active and sham treatment groups could improve or have no improvement. While nothing suggests this is likely, ADHD symptoms or other behaviors could also worsen. Finally, if your child improves during the study it is unknown how long improvements will last.

Risks of Breaches in Confidentiality: There is a rare possibility, as with any research study, that confidentiality will be breached and that individuals outside the study team will obtain information about you.

Unknown risks and discomforts:

TNS might have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

ARE THERE ANY BENEFITS IF I PARTICIPATE?

Possible benefits to me:

The possible benefits you may experience from being in this study include improvement in your child's ADHD and other behaviors. Your child will also receive an assessment that could be useful in school planning.

Possible benefits to others or society:

If this research is successful it will provide a basis for larger studies of TNS in ADHD. Ultimately, this could lead to a non-medication treatment for ADHD that has minimal risks to patients.

WHAT OTHER CHOICES DO I HAVE IF I DON'T WANT TO PARTICIPATE?

Standard treatment for ADHD usually includes medication and might also include parent training, social skills training, and accommodations at school. FDA approved medications include stimulants, such as Concerta and Adderall, and non-stimulants such as Strattera and Intuniv. These treatments are readily available from physicians in the community.

CAN THE RESEARCHERS REMOVE ME FROM THIS STUDY?

The researchers may end your child's participation in this study for a number of reasons, such as if his or her safety and welfare are at risk, if you do not follow instructions or if you miss scheduled visits.

You can stop being in the study at any time. If you decide to stop being in the study, or are removed from the study, we would ask that you return for one final visit so that you

can return any equipment and supplies and so that we can check and be sure your child's health is OK.

HOW WILL INFORMATION ABOUT ME AND MY PARTICIPATION BE KEPT CONFIDENTIAL?

Use of personal information that can identify you:

We will need to collect some personal information from you so that we can contact you about study visits and requirements. We will also ask your permission to call you in the future if there is another study you might qualify for. This information will be kept in a locked file that is only available to study staff.

How information about you will be stored:

Research data from this study will be entered into an electronic database that is protected by a password. Only information that is important for this research will be entered into this database. Your data will be identified by a code only and will not be directly linked to anything that could identify you.

People and agencies that will have access to your information:

In general, only the research team will have access to any information about you. Authorized UCLA personnel and regulatory agencies such as the Food and Drug Administration (FDA), may have access to study data and records to monitor the study. Any information from this research project that personally identifies you will not be released or disclosed by these agencies without your separate consent, unless required by law. Research records provided to authorized, non-UCLA personnel will not contain identifiable information about you. Publications and/or presentations that result from this study will not identify you by name.

How long information from the study will be kept:

Once the study ends, we will destroy any personal data that is linked to your research records. Research data will be kept for as long as it seems to be useful to answer related scientific questions.

In the future, data collected for this study may be shared with other researchers for other studies that are unknown at this time. This may include placing your data on government sponsored publically accessible research databases. Any data shared with other researchers, will not include your name or other personal identifying information.

ARE THERE ANY COSTS FOR TAKING PART IN THIS STUDY?

There is no cost to you or your insurance for participation in this study. If at the end of the study you arrange for ongoing treatment in the UCLA ADHD clinic or other clinic program, you will be responsible for usual costs associated with standard medical care.

Participants and families will not be financially responsible if the device is lost, broken, or stolen.

WHO OWNS MY CHILD'S DNA SAMPLE?

Your child's saliva will be used to analyze DNA and these analyses will be used to help understand how genes affect behavior. This DNA sample, along with any commercial products that might be derived or developed from the sample, will be the property of the University of California. Neither you nor your child will have any ownership of commercial properties developed from the sample.

WILL I BE PAID FOR MY PARTICIPATION?

You will be provided with a voucher for UCLA parking at each visit. You will also be given a \$10 stipend at each visit to cover time and other related expenses of participation. You will be given an additional \$10 after completion of each of the two EEGs and an additional \$10 on the 4 visits when your child completes tests on the computer. Finally, your child will have the opportunity to earn up to \$25 during the computer game administered at Visit 4. It is expected that your child will be given some or all of this compensation, at an amount you determined is appropriate. The total compensation if your child completes all study visits is \$155, or \$175 if you are eligible and opt to participate in the 4 week open-label treatment phase at study end.

We will continue to provide free parking for families that continue in the one year extension study, but we will not provide additional stipends for those visits.

WHAT OTHER THINGS SHOULD I CONSIDER BEFORE PARTICIPATION?

Researcher Financial Interests in this Study

UCLA has a patent on the use of the stimulator and might eventually receive financial benefits if it proves useful in ADHD. However, study investigators will not benefit financially from the results of this study.

WHO CAN I CALL IF I HAVE QUESTIONS ABOUT THIS STUDY?

The Research Team:

You may contact Jennifer Cowen at 310-825-6170 with any questions or concerns about the research or your participation in this study. After hours or on weekends, you can also reach the study investigator Dr. McGough through the UCLA page operator at 310-825-6301 if any emergencies arise.

UCLA Office of the Human Research Protection Program (OHRPP):

If you have questions about your rights while taking part in this study, or you have concerns or suggestions and you want to talk to someone other than the researchers about the study, you may contact the UCLA OHRPP by phone: (310) 825-5344; by email: mirb@research.ucla.edu or U.S. mail: UCLA OHRPP, 11000 Kinross Ave., Suite 102, Box 951694, Los Angeles, CA 90095-1694.

Public Information about this Study:

ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You can choose whether or not you want your child to participate. Whatever decision you make, there will be no penalty to you and you will not lose any of your regular benefits.

- You have a right to have all of your questions answered before deciding whether to take part.
- Your decision will not affect the medical care you receive from UCLA.
- If you decide to take part, you can leave the study at anytime.
- If you decide to stop being in this study you should notify the research team right away. The researchers may ask you to complete some procedures in order to protect your safety.
- If you decide not to take part, you can still get medical care from UCLA.

HOW DO I INDICATE MY AGREEMENT TO PARTICIPATE?

If you want to participate in this study you should sign and date below. You have been given a copy of this consent form and the Research Participant’s Bill of Rights to keep.

- I agree to be contacted in the future if there is another study I might be interested in or eligible for. _____ (Initial)
- I do not want to be contacted for future studies. _____ (Initial)

SIGNATURE OF THE PARENT

Name of Participant

Name of Parent

Signature of Parent

Date

SIGNATURE OF PERSON OBTAINING CONSENT

Name of Person Obtaining Consent

Signature of Person Obtaining Consent

Date