RESEARCH PROTOCOL

TITLE: The Effects of *ProFoveate* ™ on Reducing Self- Stimulating Behaviors In Children Diagnosed With Autism Spectrum Disorders

PRINCIPAL INVESTIGATOR: Samuel Atcherson, Ph.D.
Associate Professor, UALR/UAMS
Department of Audiology and Speech Pathology/CHP
Email: sratcherson@ualr.edu
Office Phone: 683-7178
FAX: 501-569-3157

Co-INVESTIGATOR: Betholyn Gentry, Ph.D.
Professor, UAMS/UALR
Department of Audiology and Speech Pathology/CHP
Email: gentrybetholynf@uams.edu
Office Phone: 569-8913
FAX: 501-569-3157

Study Physician: Eldon Schulz, M.D.
Professor, Department of Pediatrics/ COM
Telephone: 364-1836
schulzeldon@uams.edu

Medical Monitor: Tom Wells, M.D., M.B.A.
Professor, Department of Pediatrics/ COM
Telephone: 603-1638
E-mail: wellsthomasg@uams.edu

LOCATION: University of Arkansas at Little Rock Speech and Hearing Clinic

RESEARCH PLAN

Background and Significance/Rationale

Autism Spectrum Disorder (ASD) is a developmental neurological disorder that impairs basic behaviors such as communication and social interactions and often manifests itself in restricted or repetitive behaviors (American Psychiatric Association, 2000). The word "spectrum" accurately defines this disorder as it can range from severe impairment to mild dysfunction. In recent years, the number of children diagnosed with Autism Spectrum Disorder has increased, with the latest prevalence figures estimating an average of 1 in 50 children (Centers for Disease Control and Prevention [CDC], 2013). ASD is characterized by impairment in communication skills, social interaction, and behavior. As the overall prevalence has continued to rise, so has the demand for innovative intervention (Fombonne, 2005; Newschaffer, Falb, & Gurney, 2005; Rice, 2009; Wing & Potter, 2002; Smith, Press, Koenig, and Kinnealey, 2005; Sutherland & Crewther, 2010).

Among the many challenges for individuals with ASD is the tendency to engage in self-stimulating, or stereotypic behaviors. Often these behaviors can pose deterrents to social interaction with typical peers, especially for high functioning (HF) individuals with ASD. For the purpose of this study individuals with high functioning ASD have average to above average intelligence. Self-stimulating behaviors can serve as coping mechanisms for the individual with ASD and may pose a life long struggle. These behaviors can be a major concern to parents, peers, and professionals working with this population of individuals. Researchers have examined self-stimulating behaviors for several years. Harris & Wolchik (1979) identified several self-stimulating behaviors in children with autism which included behaviors like hand flapping, twisting ear, finger manipulations, and repetitive rubbing of hands and face. Turner (1999) divided these self-stimulating into lower level behaviors that are characterized by repetition of movement, and more complex and high-level behaviors that are characterized by object attachment and insistence on sameness. Later, Kennedy, Meyer, Knowles, & Shukla (2000) reported that in some individuals these behaviors are associated with environmental stimulation, and in other individuals these behaviors are associated with negative reinforcement and the absence of environmental stimulation. Militerni, et al, (2002) found that the majority of the children with ASD exhibited more than one repetitive behavior. Therefore, management of self-stimulating behaviors can impact the quality of life for individuals with ASD. Several techniques have been tried to eliminate self-stimulating behaviors in individuals with autism with varying degrees of success: time out, overcorrection, differential reinforcement of other behaviors (Harris & Wolchik, 1979); behavior modification (Matson & Lovullo, 2010); exercise (Watters & Watters, 1990; Rosenthal-Malek & Mitchell, 1997); and weighted vest (Fertel-Daly, Bedell & Hinojosa 2001). More recently, Smith, Press, Koenig, and Kinnealey (2005) found that repetitive behaviors were reduced after Sensory Integration therapy. We are interested in applying a new intervention procedure called ProFoveate™.

ProFoveate™ intervention for nystagmus is a management approach comprised, in part, of non-magnetic, 1.2 mm steel spheres (see below) placed strategically about the face and ears and a set of exercises designed to support improved vision for patients with nystagmus. The developers have shown in a provisional patent that the strategic placement of the press pellets or patches containing one or more pellets, which may be affixed to the skin of the patient, can greatly enhance the visual acuity of the wearer with nystagmus. Studies have shown that children with ASD and children with nystagmus share a resistance to post-rotary nystagmus (Happe & Frith, 1996; Nelson, Nitzberg & Hallander, 1980; Ornitz, Brown, Mason & Putman, 1974). Responses to vestibular stimulation such as that provided by rotary testing of the individual can provide an assessment of brain stem function. Ornitz, Atwell, Kaplan & Westlake, 1985) found that children with autism had significantly longer time constants during the

primary nystagmus response and significantly fewer beats during the secondary response than normal children when stimulated with constant angular acceleration in complete darkness. The greater length of time shows the resistance to nystagmus in this group. It is believed that enhanced stimulation of the Occiput point, which is best accessed behind the ear, could reduce self-stimulating behaviors in children with autism and increase a sense of calm more conducive to learning and social interaction. Roussi, et. al., (2011) demonstrated the importance of electrophysiological measures in making a diagnosis in patients with congenital nystagmus. Congenital nystagmus is an ocular oscillation that usually appears in early infancy. It is most often, but not always, seen in association with visuosensory abnormalities (Gelbart & Hoyt, 1998). ProFoveate™ has provided the visual acuity often sought through surgery in patients diagnosed with congenital nystagmus. The potential use of this product in patients with autism has not been explored to date. There is some evidence in the literature to suggest that vestibular stimulation may have an impact on behavior and neural activity in children with ASD (Grandin, 1996; Ornitz et.al., 1985; Ornitz, Guthrie & Farley, 1977; Ornitz, Brown, Mason & Putnam, 1974; Miller, Reisman, McIntosh, & Simon, 2001; Ray, King & Grandin, 1988). However, this study represents a unique application of the ProFoveate™ pellets and has the potential to help individuals with ASD manage self-stimulating behaviors like hand flapping, eye blinking, rocking, staring, etc., which can be deterrents to social interaction.

Individuals diagnosed with Autism spectrum disorders (ASD) often show patterns of restrictive and repetitive behaviors, reflecting a difficulty to inhibit excess sensory information in the brain. This information suggests sensory gating may be affecting some of the visible symptoms of ASD (Perry, Minassian, Lopex, & Lincoln (2007). Sensory gating describes neurological processes of filtering out redundant or unnecessary stimuli in the brain from all possible environmental stimuli, and prevents an overload of irrelevant information in the higher cortical centers of the brain. Current research on this topic is limited. An established method of evaluating brain activity is the use of event-related potentials (ERPs). ERPs are positive and negative voltage fluctuations (or *components*) in ongoing electroencephalograms (EEG) that are time-locked to the onset of a sensory, motor, or cognitive event. ERPs reflect brain activity that is specifically related to some stimulus or other event. ERPs are voltage fluctuations that are associated in time with some physical or mental occurrence. These potentials can be recorded from the human scalp and extracted from the ongoing electroencephalogram (EEG) by means of filtering and signal averaging (Picton et al., 2000). The results of EEG can be useful in documenting any changes in neural activity following the ProFoveate™ intervention.

Protocol Summary

Specific Aims/Objectives

The purpose of this study is to document the effects of ProFoveate™ intervention on the occurrence of self-stimulating behaviors and social skills in children diagnosed with high functioning autism spectrum disorders (HFASD). This study can potentially help researchers understand how to help reduce socially distracting self-stimulating behaviors in this group. There may even be evidence that changes in behavior may be reflected in changes in the brain.

The specific aim of this study is to:

1. Examine and describe the impact of the ProFoveate™ intervention on parents' perceptions of self-stimulating behaviors and social interaction skills in their children diagnosed with HFASD and document any changes in brain activity.

Specific Research questions are:

1. Are there differences between the HFASD experimental and HFASD control group in the occurrence of self-stimulating behaviors as reported by caregivers, following ProFoveate™ intervention?
2. Are there differences between the HFASD experimental and HFASD control group in social interaction skills as reported by caregivers, following ProFoveate™ intervention?
3. Are there electrophysiological changes in the brains of individuals with HFASD in the control group compared to HFASD individuals in the experimental group, as measured by EEGs following ProFoveate™ intervention?

The long term goal of this line of research is to determine if the supposition that the ProFoveate™ intervention is beneficial to children with HFASD is substantiated by evidence from parent report of changes in self-stimulating behaviors and social interaction skills as well as by measures of change in neural activity in the experimental group. The first step in this process is to conduct a pilot study. Depending on the findings of this pilot study, future studies may be conducted with modifications to the procedures and more participants.

Test Article

Investigational Device

ProFoveate™ intervention for nystagmus is a management approach comprised of non-magnetic, 1.2 mm spheres that can be made from either stainless steel, gold or silver plated stainless steel or titanium, placed strategically about the face and ears and a set of exercises designed to support improved vision for patients with nystagmus. The spheres chosen for this study will be five pellet patches. We decided to use five pellet patches to ensure proper placement on the occiput with our target minor population. These multi pellet patches are 0.5" x 0.5" adhesive plasters that contain latex. Each patch features a geometrically spaced cluster of five 1.2 mm silver plated pellets. They are available from Lhasa OMS at http://www.lhasaoms.com/ and come in packet of 50 pellets. We will give each participant one packet of 50 five pellet patches which will be enough for the study time frame. Any unused pellets will be returned. Individual patches (with adhesive tape) are removed from the backing as needed according to the prescribed treatment regimen. (See Figure 1)

Figure 1: ProFoveate Five Pellet Patches http://www.lhasaoms.com/

Within this study, HFASD participants assigned to the experimental group will wear the silver plated stainless steel ProFoveate™ pellets strategically placed on their ears and held in place by the adhesive tape continuously for four weeks.

Study Treatment Instructions

Parents of children assigned to the experimental group will be given instructions on how to use the ProFoveate™ pellets. The follow instructions will be included on a brochure (See supporting materials) and given to parents of children in the experimental group during visit 2:

1) The *ProFoveate™ pellets* are to be placed on the occiput of the right ear as indicated in the picture below.
2) Generally, the *ProFoveate™* pellets should be changed every 2 to 3 days or when they fall off.
3) Before applying, the skin should be thoroughly cleaned with alcohol and the tape applied with a good seal.
4) Check regularly to ensure that the pellets are in place.
5) Write down the date on the *Patient Diary Sheet* each time the pellets are checked.
6) You will be supplied with a packet of 50 pellets to use as needed during the 28 days of *ProFoveate™* intervention. All unused pellet are t to be returned during the last visit.

Parents and children will be shown exactly where to place the pellets on the ear. Specifically, the Occiput point will be identified for each participant. In traditional Chinese medicine, the Occiput point on the ear may be used to influence brain and spinal cord function. Note in particular the proximity of the vestibular nerve (yellow) to the skin anterior to the ear canal and medial to the pinna on the ear in Figure 2 below. The Occiput point we want to use is behind the ear and lateral to a projection of the vestibular nerve (Figure 3).

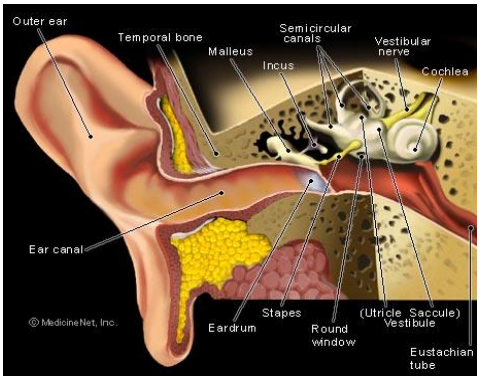

Figure 2. http://images.emedicinehealth.com/images/eMedicineHealth/illustrations/ear_cutaway.jpg

Figure 3: Occiput point on ear.

Study Treatment Compliance
Parents will be provided with a Patient Diary Sheet (see supporting documents) and will be instructed to perform and document daily checks for placement of the pellets.

Device Dispensing and Disposition

Parents of each participant in the experimental group will be given a one month supply of silver plated stainless steel pellets (50 pellets) following group assignment at the initial study visit. Used pellets (those removed each time the pellets are changed) will be discarded. Unused pellets will be returned at the final study visit.

Study Design and Procedures

Schedule of Time and Events

	Visit 1	Visit 2	Study Intervention (or no-treatment control) Period	Visit 3	Visit 4
Study Procedures	**Day 1**	**Day 2**	**Days 2-29**	**Day 30-34**	**Day 30-34**
Informed Consent	x				
Hearing Screening	x				
TONI-4	x				
Randomization	x				
SSIS – Student Form	x			x	
TOPL-2	x			x	
Parent Questionnaire	x			x	
SSIS – Parent Form	x			x	
Video Taping	x			x	
EEG		x			x
Dispense Test Article[a]		x			
Log in returned Test Article[a]					x
Study Treatment[a]		x	x		
Treatment Compliance[a]		x	x		
Adverse Event Review		x			x

EEG = electroencephalography; TONI-4 = Test of Nonverbal Intelligence 4; SSIS = Social Skills Improvement System; TOPL-2 = Test of Pragmatic Language -2

[a] Only for those subjects assigned to the experimental group

This is a pilot study aimed at examining the effects of ProFoveate™ intervention on reducing some of the hallmark characteristics of HFASD. Specifically, we are interested in documenting any changes in self-stimulating behaviors or social skills and neural activity as reported by parents and EEGs. A two group control group design will be utilized where both the experimental group and control group of individuals with HFASD will receive assessments of self- stimulating behaviors, social skills and neural activity at baseline. The experimental group will receive the ProFoveate™ intervention followed by reassessment of both the experimental and control groups at the end of the study. The target participants are 30 children diagnosed with HFASD between the ages of 10 and 17 years and their parents. This older age group was chosen because the participants must able to apply and monitor the ProFoveate™ pellets. Participants will be recruited by sending out flyers (See Flyer attachment) to autism support groups and to previous clients of a social skills program at the UALR Speech and Hearing Clinic. Participants who are interested in participating will make an appointment. At that time the consent form will be reviewed and any questions will be answered by the principal investigator. Participants will be given as much time as needed to review the consent/assent forms (See consent and assent form attachments). Those who provide consent/assent and have a documented diagnosis of ASD (autism, Asperger's syndrome, or PDD-NOS) will be assessed. Participants will come to the UALR Speech and Hearing Clinic for four visits. Visit

1 will involve the initial assessments and visit 2 will involve the initial EEG. Visit 3 will involve final assessments and visit Child participants will be assessed using the following measures: 1) hearing screening at 25 decibels for the frequencies 1000, 2000 and 4000 hertz; 2) *Test of Nonverbal Intelligence* 3 (TONI-3; Brown, Sherbenou & Johnsen, 2009; 3) *Social Skills Improvement System SSIS* - Student form (Gresham & Elliot, 2008); and 4) *Test of Pragmatic Language -2* (TOPL-2; Phelps-Terasaki & Phelps-Gunn, 2007; See Supporting Materials). All assessment procedures with each child in Visits 1 and 3 will be video recorded and analyzed using the observation of self-stimulating behaviors checklist (See Supporting Materials). Additionally, parent participants included in the study will assess their children using a standardize measure: 1) the *Social Skills Improvement System SSIS* - Parent form (Gresham & Elliot, 2008) and a non-standardized measure: 2) the *Questionnaire for Parents of Children with Autism Spectrum Disorders* (Gentry, 2013) (developed by the researcher to identify self-stimulating behaviors); to assess their children's social skills (See Supporting Materials). Both assessments will be administered at the beginning and end of the study. These assessments are expected to last 2 hours. The twenty-five self-stimulating behaviors identified as a concern for this study include: hand flapping, pulling or twisting ear, scratching, masturbating, shuffling or tapping feet, chewing clothes, picking or rubbing clothes, sucking finger, playing with hair, vocal noises, mouthing, self-injurious behaviors, head banging , rhythmic rocking, twirling objects, tongue rolling and clicking, teeth clicking, head shaking, knocking knees together, gazing at a particular object, repetitive rubbing of mouth and face, finger manipulations, locking hands behind head, grimacing , and tensing whole body and shaking.

All qualifying child participants will participate in the PI's Auditory Electrophysiology and (Re)Habilitation Lab located in the UAMS/UALR Department of Audiology and Speech Pathology and is associated with the UALR Speech and Hearing Clinic. Event-related potential (ERP) measures on a multichannel Neuroscan evoked potential system (Compumedics UCA, Charlotte, NC) will be taken twice, at the beginning and at the end of the study. ERPs are positive and negative voltage fluctuations (or *components*) that are time-locked to the onset of a sensory, motor, or cognitive event. ERPs are non-invasive and can be recorded from the human scalp using surface electrodes and extracted mathematically from the ongoing electroencephalogram (EEG) by means of filtering and signal averaging (Picton et al., 2000). ERPs have been used recently to study various phenomena in normal and disordered subject groups with encouraging results (Abel, Wang, & Dell'Osso, 2008; Andersson, Barder, Hellvin, Løvdahl, & Malt, 2008; Balaz, Rektor, & Pulkrabek, 2008; Dichter, van der Stelt, Boch, & Belger, 2006; Paul et al., 2005; Roth, 2000; Sachs et al., 2004; Sumich et al., 2008). In the proposed study, we will elicit the P300 ERP using a visual Stroop task (e.g., Rosenfield & Skogsberg, 2006) and an auditory oddball task (e.g., Edelson et al., 1999). After slight cleaning with alchohol pad and EEG skin prep cream, participants will have 8 electrolyte paste-filled electrodes (silver-silver chloride) placed on their head and secured with medical tape: 3 on the scalp as non-inverting (Fz, Cz, and Pz), 1 on each mastoid and linked as inverting input (M1 and M2), 1 on the forehead as ground (Fpz), and 1 above and below each eye as for ocular artifact rejection purposes (EOG). Electrode impedances will be checked to ensure they are 4 kohms or less. ERPs will be bandpass filtered 0.1 to 30 Hz (12 dB/oct) and sampled 200 times per second. Individual visual ERP measures will be obtained while the participant is engaged in the Stroop task (e.g., presentation of color words with a congruent [standard presented 80% of the time] or incongruent [target presented 20% of the time] color). Word stimuli (red, blue, green) will be presented via computer monitor screen and at the rate of 1.1/s (stimulus duration: 200 ms). Individual auditory ERP measures will be obtained while the participant is engaged in an auditory oddball task using 1000 Hz (standard stimuli presented 80% of the time [400 stimuli]) and 2000 Hz (target stimuli presented 20% of the time [100 stimuli]) short duration tonebursts. Tonebursts with 40 ms durations (10 ms rise/fall times) will be presented binaurally through earphones at 70 dB peak SPL at the rate of 1.1/s. For both visual and auditory ERPs (specifically the P300 response), participants will be engaged in a button-

pressing task that provides the accuracy of their responses and reaction time. Following EEG recordings, ERP analysis time windows will be set *post hoc* permitting a -100 ms pre-stimulus baseline and a post-stimulus time that extends well beyond the P300 latency (e.g., epoch of -100 to 700 ms). EEGs will undergo ocular artifact rejection and be baseline corrected prior to production of an average to all target stimuli. P300 amplitude and latency measures will also be taken. These procedures are expected to last no more than one to one and a half hours in a single session or a split session depending on the needs of the participant. During the administration of ERP procedure, the PI will not be aware if the child participant undergoing the procedure is in the control group or experimental group. This approach will support internal validity and minimize the potential for investigator bias. Sample waveforms showing several ERP components, including P300 are presented in Figures 4.

Figure 4

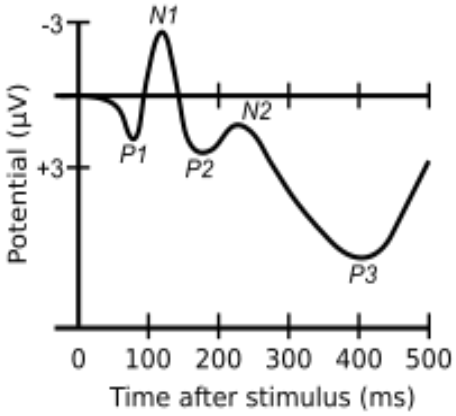

Figure 4: http://en.wikipedia.org/wiki/file:ComponentsofERP.svg

Following initial assessment, child participants will be randomly assigned to either the control group (15 participants) or the experimental group (15 participants). Participants in the experimental group will be required to wear the ProFoveate™ metal pellets held in place by small adhesive bandages strategically placed on their ears during days 2-29. Participants in the experimental will be told to return for the final assessment on days 30-34 following cessation of treatment. Participants in the control group will receive no study intervention. Participants in the control group will be told to return for final assessment on days 30-34 following initial assessment.

The null hypothesis predicts that there will be no significant change in parent perceptions of self-stimulating behaviors or social skills following the ProFoveate™ intervention. The alternative hypothesis predicts that the ProFoveate™ intervention will have a significant effect on parent perceptions of self-stimulating behaviors and social skills behaviors. Regarding the electrophysiological measure (ERP) of change in neural activation, the null hypothesis states that following ProFoveate™ intervention, there will be no measurable change in ERP measures during an accepted cognitive task. The alternative hypothesis states that there will be a measurable difference in neural activation as demonstrated by changes in P50 and P300 peak and latency measures in the ASD group receiving ProFoveate™ intervention.

Inclusion/Exclusion Criteria

A total of 30 parents and their children with ASD between the ages of 10-17 years will be recruited for this study. Participants who return consent and assent forms, must meet the following criteria to be included in the study:

Inclusion Criteria

- Have a documented diagnosis of high functioning autism spectrum disorders (autism, Asperger's syndrome, or PDD-NOS) as reported by specialists who use the established criteria (American Psychiatric Association,2000)
- Pass a hearing screening at 25 decibels for the frequencies 1000, 2000 and 4000 hertz
- Score 85 or above on the *Test of Nonverbal Intelligence- 4* (TONI-4; Brown, Sherbenou & Johnsen, 2009)
- Exhibit noticeable self- stimulating or ritualistic behaviors (i.e., scratching, hand flapping, eye blinks, etc.) and/or visual characteristics of ASD (sensitivity to light, visual fixations, poor eye contact, etc.) as reported by parents and/or observed on videos taken during assessment.

Exclusion Criteria

- Known history of latex allergy
- Score 84 or below on the *Test of Nonverbal Intelligence- 4* (TONI-4; Brown, Sherbenou & Johnsen, 2009)
- Fail the hearing screening

Ethical Considerations

The following disclosure statement will be included on consent forms: "Dr. Betholyn Gentry is entitled to royalties derived from the sale of ProFoveate™ products related to this research study. This research study could affect this financial interest. This means that the amount of royalties could increase or decrease based on the results of this study. The terms of this arrangement have been reviewed and approved by the UAMS Conflict of Interest Committee in accordance with UAMS Conflict of Interest Policies. The researchers will abide by the management plan outlined by the Conflict of Interest Committee (see attached management plan)."

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB).

The formal written consent/assent of each parent/child dyad will be obtained before any study procedure is performed. Parent and child participants will be provided a consent or assent form describing this study and providing sufficient information in language suitable for participants to make an informed decision about their participation in this study. The person obtaining consent/assent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study. The consent/assent process will take place in a quiet and private room, and participants may take as much time as needed to make a decision about their participation. Privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent/assent process. The consent form must be signed by the parent participant and the individual obtaining the consent. The assent form must be signed by the child participant. A copy of the signed consent and assent forms will be given to the parent participant, and the informed consent/assent process will be documented in each subject's research record (See Informed Consent Process Note).

Risks and Benefits

Risks Associated with ProFoveate™
Risks include the fact that the adhesives used to hold on the pellets contain trace amounts of latex. If the pellet causes the development of an abrasion, the skin should be allowed to rest 24 hours after which the pellet should be positioned at alternate positions such as shen men or point zero or P6 WRIST position. If the pellets are ingested, drink plenty of fluids and the pellets will be expelled from the body naturally.

Risks Associated with ERP Recordings
Risks associated with ERP recordings are minimal and pose no greater risk to individuals than would occur in daily life. All electronic instrumentation is appropriately grounded, all auditory stimuli are calibrated to safe auditory presentation levels, and all metal surface electrodes are cold sterilized. In the PI's clinical experience, only 1 patient in the 6 years the lab has been in existence experienced a small rash related to a reaction from the medical grade tape we use to secure the electrodes to the face. No other adverse reactions have been reported to any other products we use to prepare the skin surface for the electrodes, and the securing of electrodes to the head. Having to wear electrodes with wires hanging off the head may be disconcerting to some, but we have never experienced early termination of an ERP test because of electrode-related discomfort. Finally, having to sit and actively attend to the visual or auditory stimuli may be uncomfortable to some, but we have never experienced early termination of an ERP test because of discomfort related to our standard procedures.

Other Study Risks
It is possible that a breach of subjects' confidential information could occur. Measures will be implemented to minimize this risk as described in the Data Handling and Recordkeeping section below.

Potential Benefits
The potential benefits to science and humanity that may result from this study include the possibility of finding a treatment procedure for reducing self-stimulating behaviors in children with ASD. This study will provide information to researchers and professionals working with children diagnosed with high functioning autism to help them manage self-stimulating behaviors in this population.

Safety Assessments
Eliciting and Reporting Adverse Events: Subjects will be assessed for the occurrence of adverse events at each study visit. All adverse events occurring during the course of the study will be recorded on the Adverse Event Case Report Form and reported in accordance with the applicable regulations.

Identification of Adverse Events: An adverse event is defined as any new medical problem, or exacerbation of an existing problem, experienced by a subject while enrolled in the study, whether or not it is considered device-related by the investigator.

Relationship of Adverse Events to the investigational Device: The study physician will assess the relationship of the adverse event to the investigational device. The relationship will be assessed using the following categories:

- Definitely Related: A direct cause and effect relationship between the investigational device and the adverse event exists.
- Possibly Related: A direct cause and effect relationship between the investigational device and the adverse event has not been clearly demonstrated, but is likely or very likely.

- Unlikely Related: A direct cause and effect relationship between the investigational device and the adverse event is improbable, but not impossible.
- Unrelated: The adverse event is definitely not associated with the investigational device.

Serious Adverse Events: Each adverse event will be assessed for its seriousness using the criteria outlined below. The term serious adverse event is not synonymous with a "severe" adverse event, which may be used to describe the intensity of an event experience by the subject. An adverse event will be classified as serious if it meets any of the following criteria:

- Results in, or contributes to, a death;
- Life-threatening (i.e., the subject was, in the opinion of the investigator, at risk of death at the time of the event, but it does not include an event that, had it occurred in a more severe form, might have caused death);
- Results in permanent disability or incapacity (i.e., permanent impairment of a body function or permanent damage to a body structure);
- Requires in-patient hospitalization or prolongs hospitalization;
- Necessitates medical or surgical intervention to preclude a permanent disability or incapacity;
- Results in a congenital anomaly or birth defect.

Non-serious adverse events are all events that do not meet the criteria for a "serious" adverse event.

Severity: Each adverse event will be assessed for its severity, or the intensity of an event experienced by the subject using the following:

- Mild: Discomfort noticed, but no disruption to daily activity.
- Moderate: Discomfort sufficient to reduce or affect normal daily activity.
- Severe: Inability to work or perform normal daily activity.

Deaths: The investigator will notify the Sponsor as soon as possible, preferably within 24 hours but in no event later than 48 hours, of learning of a subject's death, regardless of whether the death is related or unrelated to the investigational drug. The investigator will attempt to determine, as conclusively as possible, whether the death is related to the device. The cause of death and the investigator's discussion regarding whether or not the death was device-related will be described in a written report.

Pre-existing Conditions: Pre-existing conditions will not be reported as an adverse event unless there has been a substantial increase in the severity or frequency of the problem which has not been attributed to natural history.

Unanticipated Adverse Device Effects: An unanticipated adverse device effect is defined as any serious adverse effect on health or safety, or any life-threatening problem, or death caused by, or associated with, a device; if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or application (including supplementary application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

If an unanticipated adverse effect occurs, the investigator will promptly notify the sponsor of such an event within 24 hours of first learning of the event. The investigator will notify the IRB of such an event as soon as possible, but no later than ten (10) working days after first learning of the event.

Statistical Plan

To determine significance in the occurrence of self-stimulating behaviors or social skills following ProFoveate™ intervention nonparametric statistics will be run on questionnaire and test data obtained from the experimental and control groups. Test data will consist of pre and post treatment standard scores obtained from the test manuals and questionnaire data will consist of pre and post treatment summative Likert scores reported by parents. In order to gather ERP data, use of the STIM^2 software, SCAN EEG analysis software and associated hardware/peripheral devices (located in the Auditory Electrophysiological (Re)Habilitation Lab of the PI) for data gathering and analysis of the P300 ERP will be utilized for each participant. There are two independent variables: control group and experimental group. There are seven dependent variables: SSIS parent scores, SSIS student scores, TOPL-2 scores, blinded P50 measures, blinded P300 measures, Parent Questionnaire scores and blinded video ratings of self-stimulating behaviors (see supporting materials). Interjudge reliability for video ratings will be established by having two observers review 25% (8) of the video recordings, document the occurrence of self-stimulating behaviors and calculating the percent agreement. These scores will be triangulated to compensate for the fact that the parent ratings are not blinded. The data will be analyzed using a 2 (group) x 3 (standardized scores) x 1 (Physiological measure) x 2 (observational measures) repeated measures multivariate analysis of variance (See Figure 5).

Data Handling and Recordkeeping

All questionnaires and test forms will be maintained by the principal investigator in a locked file accessible only to the staff of the research study for three years. Both assessment sessions with students will be video recorded for later analysis of observable self- stimulating behaviors. Only the co-investigator and Citi-certified graduate students will view the videotapes. The videotapes and assessment protocols will be maintained in a locked file in the co-investigator's lab for three years and then destroyed.

Confidentiality

No participants will be identified in any reports except by a study identification number. Participants will be assigned a number (1 - 15) and a group (control or experimental) randomly. All computerized files will be stored on password protected computers. No computerized data files will include names, addresses or phone numbers. No identifying information will be used in the study or future publications.

Study Registration and Publication

This study will be registered on the ClinicalTrials.gov website as required by law. The results of this study will be written as a manuscript and submitted for publication. The results will also be presented in abstract form at a state or regional or national speech language pathology conference by the PI and/or the Co-investigator.

References

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