AWARD NUMBER: W81XWH-18-1-0459

TITLE: Predicting Situational Onset of Aggression in Minimally Verbal Youth with Autism Using Biosensor Data and Machine Learning Algorithms

PRINCIPAL INVESTIGATOR: Matthew Siegel, MD

CONTRACTING ORGANIZATION: MaineHealth, Portland, ME

REPORT DATE: September 2021

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
September 2021	Annual	01Sep2020-31Aug2021

4. TITLE

Predicting Situational Onset of Aggression in Minimally Verbal Youth with Autism Using Biosensor Data and Machine Learning Algorithms

5a. CONTRACT NUMBER
W81XWH-18-1-0459

5b. GRANT NUMBER
AR170209P1

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Matthew Siegel, MD

E-Mail:siegem@mainebehavioralhealth.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

MaineHealth
22 Bramhall Street
Portland ME 04101

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT Unpredictable aggressive behavior by youth with autism spectrum disorder (ASD) isolates them from educational, social and family activities. Approximately 2/3 of youth with ASD display aggression, a common reason for treatment referral; yet evidence-based pharmacological and behavioral interventions for aggression in ASD are frequently ineffective. Aggression is particularly impairing in the 30-40% of youth with ASD who are minimally verbal (MV-ASD). Aggression may represent a maladaptive attempt to express or modulate physiological arousal arising from distress. We hypothesize that physiological arousal precedes aggressive behavior. We aim to predict aggression in MV-ASD before it occurs using data collected from wrist-worn physiological sensors and behavior observation. Using sophisticated machine learning algorithms linking observable aggression to preceding physiological signals (heart rate, skin conductance), we may identify new opportunities for intervention. Since project launch, we have refined data collection procedures, established processes for behavioral data upload and physiological data transfer to collaborators at NEU, and implemented physiological data quality checks. Staff training has been completed on all procedures including use of biosensors and a smartphone application to code aggression instances, at a high level of inter-rater reliability. 49 youth have been enrolled and data collection has been completed with 25 thus far.

15. SUBJECT TERMS
Autism Spectrum Disorder, ASD, Minimally Verbal, Aggression, Prediction, Physiological Arousal, Arousal Modulation, Machine Learning.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	15	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

Page

INTRODUCTION:

Unpredictable and potentially dangerous aggressive behavior by youth with autism spectrum disorder (ASD) isolates them from important educational, social, and family activities, thereby increasing the difficulties and costs associated with the condition. As many as 2/3 of youth with ASD display aggression, which is one of the primary reasons they get referred for treatment. Aggression presents serious safety risks for the individual and others in the environment and frequently occurs with agitation, meltdowns, and other problem behaviors that are difficult to manage. Families report that aggression increases their stress, isolation, and financial burden, and decreases available support options. Aggression toward others is significantly impairing and challenging to manage in the 30-40% of youth with ASD who are minimally verbal (MV-ASD). Their difficulty verbalizing distress can lead to behaviors that seem to occur without warning, sometimes long after any obvious trigger. Aggression toward others may represent a maladaptive attempt to express or modulate physiological arousal arising from distress. Thus, we hypothesize that physiological arousal precedes aggressive behavior.

Our project aims to predict aggression toward others in MV-ASD before it occurs using data collected from commercially available wrist-worn wireless physiological sensors. The unique inpatient setting where this study is taking place allows us to study aggression in a controlled, safe environment. Our project will provide predictive information (i.e., the onset of aggressive behavior in the proximal future using physiological data from the recent past) that may ultimately define new opportunities for intervention. This innovative approach has the potential to improve our ability to identify escalating distress in youth with MV-ASD, overcoming their inherent difficulty conveying feelings and emotions. By linking observable aggressive behavior to the detection of preceding physiological signals (e.g., heart rate, sweating), we hope to move the field of problem behavior assessment and treatment in autism towards a new biologically-based, data-informed approach that is focused on prospective monitoring, prevention, and eventually, real-time intervention. Since study launch, we have completed physiological data collection with 25 inpatient youth.

KEYWORDS:

Autism Spectrum Disorder, ASD, Minimally Verbal, Aggression, Prediction, Physiological Arousal, Arousal Modulation, Machine Learning

ACCOMPLISHMENTS:

What were the major goals of the project?

Goal 1: Establish physiological biomarkers of imminent aggression. We will observe and record aggression toward others in 40 MV-ASD inpatient youth during repeated naturalistic observations in an inpatient psychiatric unit while they wear biosensors that measure physiological arousal and motor activity. These data, in combination with time-synchronized coding of aggression by research staff using a mobile application, will be analyzed by machine learning algorithms to create a set of properties that predict the onset of aggressive behavior. All activity in years 1-3 were focused on Goal 1.The COVID-19 pandemic slowed enrollment and data collection with inpatient participants, so additional time is needed to complete Goal 1. With approval of a NCE, we seek to complete this goal in Year 4. Reflecting on the behavioral and communication difficulties of our inpatient youth who have Intellectual Disorder (ID) and exhibit similar impairment in verbalizing distress as our MV youth, we amended the study criteria to include children with a Nonverbal IQ below 70. This expanded the pool of youth eligible to participate in this study. To date, we have completed physiological data collection with 25 youth.
Goal 2. Evaluate the positive predictive value and reliability of imminent aggression prediction. We will apply the highest performing classifiers from Aim 1 to validate aggression prediction prospectively in an independent MV-ASD inpatient youth sample (n=20) and examine classifier performance and individuals' stability over time. With the delays in reaching our target enrollment for Goal 1 due to the pandemic, we will utilize the NCE to complete Goal 1 and recruit the independent sample for Goal 2 in year 4 of this study.

What was accomplished under these goals?

1) **Major Activities**

Note: The NU site Co-Investigator and MMC Co-Investigator were jointly responsible for all training and reliability activity *except where explicitly denoted below.

Training and Coding Reliability: In this study seeking to identify biological predictors of aggression, it is imperative to define aggression itself explicitly and to maximize the detection of this target behavior in a highly reliable and replicable manner. Low sensitivity to the target behavior, false-positive detection, or inaccurate identification of other problem behavior as aggression are errors in behavior coding that could render a prediction model meaningless.

In year 1, the study RAs received intensive training on aggression identification and direct behavior coding utilizing a mobile device application developed for this study by the NU team to record aggression instances correctly. Aggression was operationally defined as behavior that may cause injury or harm to others OR forceful physical contact with another person (Mace et al., 2009). Examples of aggressive behavior to be coded included hitting, kicking, biting, scratching, grabbing, pulling, pushing, spitting, hair pulling, headbutting, slapping, or throwing objects at people. This initial training was described in the year 1 Annual Report. Ongoing training continued during year 2 and year 3, with regular instruction and discussion as a part of the quarterly meetings described below.

As described in previous Annual Reports, a plan for inter-rater reliability (IRR) was initially developed with input from the study data analyst and included (a) **group sessions** with RAs concurrently coding prepared training videotapes and (b) *in situ* **double coding** of study participants by two RAs during 20% of their physiological data collection sessions. Since study launch and initial training, reliability recalibration sessions have been held to assess IRR and prevent coding drift, calibrating RA coding of behaviors with Co-PI Dr. Siegel as the master coder. With the COVID pandemic limiting patient contact and in person research staff meetings, IRR coding sessions have been held less frequently but in proportion to the enrollment rate. However, staff coding of problem behaviors, including aggression, emotion dysregulation (ED), and self-injurious behavior (SIB), has continued to achieve acceptable reliability compared to the master coder. We will continue this process of assessing IRR during the NCE year as enrollment dictates. As explained in previous Annual Reports, the mobile device application used by RAs for this study records the onset and offset time of each problem behavior, producing data output that captures both the occurrence and time interval. The target behaviors are coded based on the operational definitions outlined for this study, as specified in the chart below**. * Videos were created at the MMC site for training purposes, and Dr. Siegel, Co-PI, conducted the training/IRR sessions.**

Target Behavior	Definition	Examples
Aggression	Behavior that may cause injury or harm to others OR forceful physical contact with another person (Mace et al., 2009)	Hitting, kicking, biting, scratching, grabbing, pulling, pushing, spitting, hair pulling, headbutting, slapping, or throwing objects at people
Emotion Dysregulation	Perseverative agitation OR rapidly escalating, intense, or labile negative affect and difficulty calming down	Appearing angry or irritable, explosive outbursts, crying, being tense and unable to relax (agitated pacing), sudden switches to opposite emotion, extreme or intense emotional reactions, angry threats, crying, yelling/screaming, throwing self to flor, seems to be in a rage, appears on edge
Self-Injury	Behavior that may cause injury to self OR repetitive motor movements that result in injury to the person or have the potential to inflict damage (Lewis and Bodfish, 1998).	Hitting self, biting self, scratching self, poking or gouging the eye of self, banging head on surfaces, banging other body parts on surfaces, skin picking, self-slapping, pulling out own teeth

As mentioned above, part (b) of the IRR plan stipulates that two study RAs will double code behaviors during 20% of the total physio data collection time for each participant (e.g., 2 hours of every 10 hours of data collection). We expect an agreement of 80% or higher for aggression occurrence and onset and offset times based on our RA training outcomes. For all participants with data collected to date, two RAs conducted double coding for a portion of the completed sessions. As a result of the pandemic, the number of completed cases is still too low to calculate the double-coding IRR statistic as of this writing, but we hope to increase the N and complete this analysis in year 4. *** All initial and recalibration training was conducted at the MMC site.**

Study Oversight and Data Quality Checks: Over the past three years, oversight of all study procedures has been conducted by Co-PIs Dr. Matthew Siegel, Maine Medical Center, and Dr. Matthew Goodwin, Northeastern University (NU). Dr. Siegel directly supervises the RAs completing data collection at the clinical study site (Spring Harbor Hospital). Dr. Goodwin directs the bioinformatics lab at NU, and oversees the work of Natasha Yamane (Ph.D. student) and Catalina Cumpanasoiu (Ph.D. student, now matriculated) who review the quality of physiological data collected using the E4 biosensor. As reported in previous years, Co-PI and staff conference calls support the supervision and guidance of research staff as needed. * **Both sites contributed equally to oversight and ongoing communication.**

The REDCap (Research Electronic Data Capture) application continues to be used to store participant study data including tracking participation in the physiological data collection protocol and descriptive variables regarding all sessions conducted with participants. This data is entered into REDCap for each session conducted, and includes number of sessions with E4 and behavior data, session date, duration, and whether instances of aggression occurred during the session. Also entered is an indicator of biosensor data quality; provided by the NU bioinformatics staff, an alert in REDCap denotes a good or poor quality rating for E4 data collected during each session conducted. In this way, the NU team can give the clinical site RAs rapid feedback regarding data quality and any equipment issues detected. More detail regarding data quality checks is included in previous Annual Reports. *** The REDCap database and entry screens were initially created and are maintained by the Data Manager, Christine Peura, under the supervision of Dr. Siegel at the MMC site. Dr. Goodwin and the NU team contributed significantly to identifying important variables to record in REDCap and continue to access all data sources to monitor physiological data quality and pair physiological data with mobile app-collected behavioral data for each participant. As of this writing, Natasha Yamane (Ph.D. student) completes the physiological data quality reviews under Dr. Goodwin's direction at NU.**

Note: The MMC site is responsible for all enrollment and direct collection of physiological data, behavioral data, cognitive assessments, and caregiver survey data, as described below.

Study Enrollment: Since launch of data collection, all eligible patients admitted to the Developmental Disorders unit at Spring Harbor Hospital, Maine Medical Center, with known or suspected autism have been considered for participation in the study. Enrollment and data collection was slowed or halted for periods over the past year due to the COVID-19 pandemic, and resulting institutional pauses on research and challenges in working in close proximity to inpatients. These barriers have since been removed and data collection is continuing. As described, patients identified as being minimally verbal (no more than 3-word phrases) were recruited, and the guardian offered the option of consenting to the study. We also expanded enrollment to recruit and consent inpatient youth with ASD and Intellectual Disorder (non-verbal IQ less than 70). As of this writing, we have consented 49 children in total. Although consented, data collection may have been halted due a child's inpatient stay being too short, due to a COVID related research pause, or because a child had difficulty tolerating the wrist worn biosensor. Of the 49 consented to date, we have completed data collection with 25. However, the remaining children (for whom we have consent but not complete data) can be assessed if re-admitted to the hospital during the NCE year. For a small group of children who could not tolerate wearing the biosensor, additional desensitization sessions can be conducted to increase their comfort with the protocol and biosensor tolerance, should they be re-admitted in the next year.

Measures and Forms: As in previous years, data have been collected for all participants on measures including the Social Communication Scale (SCQ); ADOS-2; Leiter International Performance Scale III; Peabody Picture Vocabulary Test-3 (PPVT-3); Emotion Dysregulation Inventory (EDI); Behavior Problems Inventory (BPI-01) Aggression/Destructive Behavior subscale and Self-Injurious Behavior subscale; and the Vineland Adaptive Behavior Scales–3, with the Vineland 3 Expressive Communication Scale line items explicitly used to quantify the level of spoken language and confirm participant MV status.

Additional data collection forms developed for the study include a Desensitization Session Data Form (for tracking desensitization success, failure, device tolerance, and practical measures employed such as verbal encouragement and use of reinforcers); Physiological Data Collection Form (for tracking completed sessions, date, duration, use of sport band/sleeves, and occurrence of any aggression); Behavior Session Note Sheet (for noting Empatica-generated session ID, types of aggression observed, such as kicking, biting, grabbing, and any reasons for gaps in data such as participant temporarily out of view or device accidentally turned off). A data collection session Preparation Checklist is also used by the RAs to ensure the complete, successful administration of the protocol, with reminders for charging and calibrating equipment, accurate file naming, etc.

2) Specific Objectives

Aggression to others may represent a maladaptive attempt to express or modulate physiological arousal arising from distress. Thus, we hypothesize that physiological arousal precedes aggressive behavior. Our objective is to reduce the impact of aggression to others in MV-ASD and ID-ASD by validating preceding physiological biomarkers. In our preliminary work (pilot study before this award), we overcame challenges to assessing this population by identifying standardized questionnaires validated for MV-ASD and ID-ASD, developing a protocol for observational timestamped coding of aggression, and measuring physiological arousal using validated wrist worn biosensor technology. As described in our proposal and Annual Reports for this study, we seek to increase prediction time and accuracy by refining our analytical methods and employing them on a larger scale to test performance generalizability across patients and classification stability within patients over time. To this end, as stated in Goal 1, we aim to recruit, observe, and record aggression in 40 MV-ASD/ID-ASD inpatient youth during repeated naturalistic observations in an inpatient psychiatric unit while they wear the Empatica E4 biosensor that measures physiological arousal. As explained above, we have not met this specific objective due to the significant impact of COVID-19 on our ability to complete hands-on data collection with children admitted to the hospital. However, we have consented 49 children and conducted data collection with 25 of them. Those children who do not have full data collected can be re-assessed if they are re-admitted to the unit during the NCE year, as we continue to also recruit and consent new eligible inpatients in the coming months.

3) Significant results or key outcomes

There are no further analytic results to report at this stage of data collection than what is already described and cited above. Key progress includes the procedural, reliability, and data quality infrastructure described above, ensuring continued success with data collection over the remaining study term, as well as a successfully overcoming COVID related hurdles to manage continuation of data collection with appropriate safety measures in place.

Note: Both NU and MMC sites are jointly responsible for the remaining material described below.

4) Other Achievements

Achievements are summarized in the above sections. There are no other achievements to report.

What opportunities for training and professional development has the project provided?

This project was the predominant focus of a doctoral dissertation completed by Catalina Cumpanasoiu at NU, who successfully defended and graduated with her Ph.D. in August 2020. The behavioral and physiological data collection research at the MMC site also provided significant training for Post-Doctoral Fellow, Briana Taylor, Ph.D. She incorporated these aspects of our project into a funded NICHD K99R00 grant application to study sleep and circadian rhythm in children with severe autism.

How were the results disseminated to communities of interest?

No dissemination yet. We plan to publish papers on our methodology and the results in late 2021.

What do you plan to do during the next reporting period to accomplish the goals?

We will continue to recruit, enroll, and conduct data collection with MV-ASD and ID-ASD youth admitted to the inpatient unit at Spring Harbor Hospital. Despite the COVID-19 pandemic, we have managed to consent 49 youth and collect data from 25. We seek to increase our enrollment of new inpatients with MV-ASD or ID-ASD (and collect data with any consented children who may be re-admitted) now that we have safe procedures in place for data collection. Having approval for a NCE year allows us the opportunity to move our numbers closer the goals envisioned, and as a result, achieve the N that will allow us to complete planned analyses.

IMPACT

What was the impact on the development of the principal discipline(s) of the project?

At this stage of study progress, it is too early for formal data analysis and disseminating results to the research community. However, as stated in our application, this study has tremendous potential to impact intervention for autism aggression. Aggression to others is typically treated in individuals with ASD with medication; however, medication can have significant side effects and inconsistent success. There are also evidence-based behavioral interventions for aggression in ASD. Still, their effectiveness is often reduced due to the inability to predict the onset of aggression, giving insufficient time to attempt de-escalation strategies. The bio-behavioral data we are collecting and the analytic models being developed in this project could enable new opportunities for intervention before distress escalates to aggression, furthering our ultimate goal of increasing safety, reducing burden on families and caregivers, and preserving the ability of individuals with MV-ASD and ID-ASD to be able to access the interventions and educational activities they need.

Our unique inpatient setting allows us to study aggression in a controlled, safe environment. Resulting data are thus ecologically valid and overcome substantial challenges associated with studying aggression in other settings. We also take advantage of technological advances with our combination of wearable biosensors and machine learning algorithms. This innovative approach holds invaluable translational potential, given the inherent difficulty obtaining reliable self-reports on emotional states from MV-ASD and ID-ASD individuals. By linking observable aggressive behavior to the detection of preceding physiological signals, we hope to move the field of problem behavior assessment and treatment in ASD towards an approach focused on prospective monitoring, prevention, and real-time intervention to mitigate the impact of aggression. The sophisticated strategies developed in this study also can potentially impact the conduct of aggression research with ASD youth itself.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Results are not yet available at this stage of our research. However, the innovative approach utilized in this study can improve our ability to identify escalating distress in minimally verbal individuals with autism, overcoming their inherent difficulty conveying feelings and emotions. By linking observable aggressive behavior to the detection of preceding physiological signals (e.g., heart rate, sweating), this paradigm has the potential to move clinical intervention for challenging behavior in autism towards a new biologically-based, data-informed approach that is focused on prospective monitoring, prevention, and eventually, real-time intervention, potentially sidestepping the side effects and inconsistent results of more traditional pharmaceutical and behavioral interventions. It is conceivable that such impact could also translate to supportive technology-based scaffolding for classroom teachers, primary care physicians, dental care providers, behavioral health care workers, and case managers in their care of minimally verbal individuals with autism and problem behavior.

CHANGES/PROBLEMS:

Changes in approach and reasons for change

We have expanded our eligibility criteria to include youth with ASD and Intellectual Disorder (ID-ASD). This step was in recognition that children with ID-ASD often have similar challenges with behavior and with communicating distress as MV-ASD children, very much fitting into our existing objective to improve prediction of aggression.

Actual or anticipated problems or delays and actions or plans to resolve them

As described previously, our enrollment and data collection completion is lower than expected due to the COVID-19 pandemic. We faced an institutionally mandated pause in data collection from March to September 2020 due to the pandemic. Overcoming barriers and delays, we successfully re-started data collection and now have collected data with 25 children. We are currently continuing to recruit and enroll MV-ASD and ID-ASD inpatients with COVID-safe measures in place.

Changes that had a significant impact on expenditures

There were no changes that affected expenditures.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

No significant changes in protocol, no deviations, no unexpected outcomes. Maine Medical Center IRB continuing review approval was granted on 6/8/2021, expiration date is 6/7/2022. Human participants are not enrolled at NU, and thus no IRB approval is required.

Significant changes in use or care of vertebrate animals

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

PRODUCTS:

Publications, conference papers, and presentations

Journal publications.

Nothing to Report.

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers and presentations.

Nothing to Report.

Website(s) or other Internet site(s)

Nothing to Report.

Technologies or techniques

Nothing to Report.

Inventions, patent applications, and/or licenses

Nothing to Report.

Other Products

Nothing to Report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Matthew Siegel, MD*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1.0*
Contribution to Project:	*Provided overall scientific direction including enrollment, data collection, analysis, and supervision of staff.*
Funding Support:	*The Simons Foundation and Nancy Lurie Marks Foundation provided additional, complementary support toward this project, as explained in materials submitted to the DoD; these foundations provide additional funding to open more sites and enroll more patients.*
Name:	*Nicole Martin*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*4.0*
Contribution to Project:	*Conducted the study protocol and collected data.*
Funding Support:	

Name:	*Charlotte Beaulieu*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6.0*
Contribution to Project:	*Conducted the study protocol and collected data.*
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

No other partners, but this was a collaborative grant with Northeastern University. A separate report is being filed by Northeastern University, per instructions.

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

This grant is a collaborative award with Northeastern University (M. Goodwin, PI). Per instructions, Northeastern University is submitting a separate report.

QUAD CHARTS:

A quad chart is attached.

APPENDICES:

There are no abstracts or papers to include at this time.