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

REPORT DATE: December 2022

TYPE OF REPORT: Final

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

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to NEU collabora	tors via the cloue	d, and phenotypic	data was transferr	ed to NEU co	ollaborators via REDcap.		
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INTRODUCTION:

Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

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. We completed behavioral, phenotypic and biological data collection with 25 inpatient youth.

KEYWORDS:

Provide a brief list of keywords (limit to 20 words).

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

ACCOMPLISHMENTS:

The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

<u>Goal 1</u>: 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. 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. All activity at the Maine Medical Center site in years 1-4 (including the NCE) was focused on Goal 1. The COVID-19 pandemic significantly slowed enrollment and data collection with inpatient participants, which continued into the NCE period. We completed physiological, phenotypic and behavioral data collection with 25 youth.

<u>Goal 2</u>. 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. Work for this goal was not performed at the Maine Medical Center site.

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

1) Major Activities

<u>Training and Coding Reliability:</u> 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. Reliability recalibration sessions were 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 were 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. 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 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.

<u>Study Oversight and Data Quality Checks</u>: Over the past three years plus the NCE period, oversight of study procedures at Maine Medical Center was conducted by Dr. Siegel. Dr. Siegel directly supervised the RAs completing data collection at the Maine Medical Center site (Spring Harbor Hospital).

The REDCap (Research Electronic Data Capture) application was 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 was 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 was 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 gave the MMC RAs rapid feedback regarding data quality and any equipment issues detected. 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.

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.

<u>Study Enrollment</u>: 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 were considered for participation in the study. Enrollment and data collection was slowed or halted for significant periods throughout the project due to the COVID-19 pandemic.

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 expanded enrollment to recruit and consent inpatient youth with ASD and Intellectual Disorder (non-verbal IQ less than 70). We 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, we completed data collection with 25.

<u>Measures and Forms</u>: Data was 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 aimed 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 wore the Empatica E4 biosensor that measures physiological arousal. As explained above, we did not meet 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, and the very slow rate of admissions to the hospital due to the pandemic. We consented 49 children and completed data collection with 25 of them.

3) Significant results or key outcomes

Key outcomes at the MMC site from the study was the development of the procedural, reliability, and data quality infrastructure described above, and the development of desensitization procedures for the successful wearing of the physiologic sensors by 25 children.

4) Other Achievements

There are no other achievements to report.

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

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 the 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?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

No dissemination yet. We have drafted a paper on desensitization techniques to collect physiologic data in this challenging population, which we plan to submit for publication in the coming months.

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

If this is the final report, state "Nothing to Report." Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Nothing to report.

IMPACT

Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

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

If there is nothing significant to report during this reporting period, state "Nothing to Report." Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

The study may impact the understanding of investigators on how to perform research with youth with autism who have challenging behaviors and are minimally verbal and/or have intellectual disability. Specifically, it may increase knowledge on how to collect physiologic and behavioral data with this population.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report.

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state "Nothing to Report." Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- transfer of results to entities in government or industry;
- instances where the research has led to the initiation of a start-up company; or
- *adoption of new practices.*

Nothing to report.

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state "Nothing to Report." Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or
- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

CHANGES/PROBLEMS:

The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report

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

Describe problems or delays encountered during the reporting period 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 collected data with 25 children. We were unable to reach the target of Goal 1 of 40 inpatients due to very slow admissions to the inpatient unit due to the ongoing pandemic. We did not enroll the independent sample of Goal 2.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

There were no changes that affected expenditures.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

No significant changes in protocol, no deviations, no unexpected outcomes for human subjects. Maine Medical Center IRB continuing review approval was granted on 05/24/2022, expiration date is 05/23/2023.

Significant changes in use or care of vertebrate animals

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

PRODUCTS:

List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

Publications, conference papers, and presentations

Report only the major publication(s) resulting from the work under this award.

Journal publications. List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to Report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study,*

commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to Report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to Report.

Website(s) or other Internet site(s)

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report.

Technologies or techniques

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report.

Inventions, patent applications, and/or licenses

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report.

Other Products

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- data or databases;
- *physical collections;*
- audio or video products;

- *software;*
- models;
- educational aids or curricula;
- *instruments or equipment;*
- research material (e.g., Germplasm; cell lines, DNA probes, animal models);
- *clinical interventions;*
- *new business creation; and*
- other.

Nothing to Report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Name:	Matthew Siegel, MD		
Project Role:	Co-Principal Investigator		
Researcher Identifier (e.g. ORCID ID):			
Nearest person month worked:	0.23 Calendar Month		
Contribution to Project:	Provided overall scientific direction at the MMC site including enrollment, data collection, and supervision o staff.		
Funding Support:			
Name:	Nicole Martin		
Project Role:	Research Assistant		
Researcher Identifier (e.g. ORCID ID):			
Nearest person month worked:	6.0 Calendar Month		
Contribution to Project:	Screened for additional subject enrollment during NCE period, worked on manuscript describing desensitization procedures.		
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?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

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, Co-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.

Predicting Situational Onset of Aggression in Minimally Verbal Youth with Autism Spectrum Disorder Using Biosensor Data and Machine Learning Algorithms ERMS/Log Number AR170209P1 Award Number W81XWH-18-1-0459 Annual Research Performance Progress Report **PI:** Matthew Siegel, MD **Org:** Maine Medical Center **Award Amount:** \$314,675



Study/Product Aim(s)

Aim 1: Establish physiological biomarkers of imminent aggression in minimally verbal youth with Autism Spectrum Disorder (MV-ASD).
Aim 2: Evaluate the positive predictive value and reliability of imminent aggression prediction.

Approach

Toward Aim 1, we will observe and record aggression in 40 MV-ASD youth in an inpatient psychiatric unit while they wear wireless autonomic biosensors that measure physiological arousal. These data, in combination with time-synchronized coding of aggressive behavior, will be analyzed by machine learning algorithms to create a set of properties to predict imminent aggression ('classifier'). To achieve Aim 2, 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 stability within individuals over time.

Timeline and Cost

Activities Funding year	2018/2019	2019/2020	2020/2022
Refine data collection procedures and establish aggression detection reliability			
Enroll & collect data from 40 subjects to develop aggression prediction classifier			
Estimated Budget (\$K)	101,083	105,197	108,395

