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

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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. 30 MV-ASD youth have been enrolled and data collection has been completed with 10.

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

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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. This unpredictability makes aggression toward others in MV-ASD dangerous and presents a barrier to accessing the community. Evidence-based pharmacological and behavioral interventions for ASD aggression are frequently ineffective due to significant medication side effects or insufficient time to provide de-escalation strategies. 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 with 24-hour access to patients for an average of three weeks each. 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.

In year 1 of this project, data collection protocols and Research Assistant (RA) training were developed, inter-rater reliability (IRR) established for coding of behavior, IRB approval was obtained, and study recruitment commenced. We conducted the protocol with 14 MV-ASD children, and physiological data were successfully collected from 8 of them. In year 2, 16 additional children enrolled, but due to institutional data collection halting due to COVID-19, we could complete data collection with only 2 participants. We now have institutional approval to resume data collection as of September 15, 2020. We are further working on desensitization techniques to increase tolerance wearing the device for this highly impaired population.

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.

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 validated wireless autonomic biosensors that measure physiological arousal (i.e., cardiovascular and electrodermal) and motor activity. These data, in combination with time-synchronized coding of aggression and non-aggression by research staff using a mobile application, will be analyzed by machine learning algorithms to create a set of properties (a "classifier") that predict imminent aggression (i.e., the onset of aggressive behavior in the proximal future using physiological data from the recent past). All activity in years 1 and 2 were focused on Goal 1.

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. Due to delays in reaching our target enrollment for Goal 1 due to institutional restrictions on data collection that have now resolved, we will complete recruitment for Goal 1 in the first half of year 3 and recruit the independent sample for Goal 2 in the 2nd half of the year.

What was accomplished under these goals?

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

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

Training: 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 (located at the MMC clinical data collection site) 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. The RAs attended a 2-day workshop on October 2-3, 2018. They received education and coding training from Co-PIs Matthew Siegel, MD, and Matthew Goodwin, Ph.D., as well as study consultant Carla Mazefsky, Ph.D., University of Pittsburgh Medical Center. 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. Further detail regarding this initial training early in year 1 is described in the year 1 Annual Report. Ongoing training continued during year 2, with regular instruction and discussion as a part of the quarterly meetings described below.

Reliability: 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. The group sessions included a pre-data collection inter-rater reliability workshop in February 2019 (coding of 10 videos), for which Dr. Siegel served as the master coder. After that, quarterly reliability recalibration sessions (coding 3-4 videos per meeting) were held in July 2019, October 2019, March 2020, and September 2020 to assess IRR and prevent coding drift. These quarterly IRR sessions will continue for the duration of the study. In all of these group sessions, the RAs independently code videos recorded for this study with consented ASD participants engaging in problem behaviors, including aggression, emotion dysregulation (ED), and self-injurious behavior (SIB). While the key target behavior of interest for this study is aggression, we are coding instances of these other behaviors based on the observation that ED and SIB can sometimes co-occur, precede, or follow aggression. We seek to understand these relationships better. The RAs perform the behavioral coding for each video using the mobile device application. We then compare their behavioral coding to a master coder (co-PI, Dr. Siegel, a child psychiatrist with over 15 years of experience assessing problem behaviors in youth with ASD in the inpatient setting). When coding an instance of a target behavior by an on/off button press, the mobile device application records the onset and offset time of each 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

The resultant data from all IRR coding sessions (initial meeting and quarterly recalibrations) are processed to eliminate intervals between offset and onset of behavior that were less than 10 seconds, as these represented either a momentary recording error by the rater or convey a brief pause in an episode of behavior that is not clinically meaningful. IRR between the RAs and the master coder are assessed by analyzing each recorded behavior's concordance of the onset times. Traditional reliability metrics cannot be calculated due to the absence of a true-negative group. As reported in the year one progress report, congruence between raters and the master coder for the initial training/IRR meeting was determined to be accurate at a sensitivity of 96.3% (range 88.9% - 100%) and a positive predictive value of 77.0% (range 64% - 85.7%). Quarterly IRR recalibration sessions were held in July 2019, October 2019, March 2020, and September 2020, and included viewing 3-4 videos per meeting and coding behaviors using the mobile application. Based on these quarterly assessments, IRR within the coding group and compared to the master coder continues to be adequate.

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. Currently, the number of completed cases is too low to calculate the double-coding IRR statistic. We will calculate them once an adequate number is collected. *** All initial and recalibration training was conducted at the MMC site. All reliability analyses were performed by James Heathers, Ph.D., at the NU site under Dr. Goodwin's supervision, Co-PI.**

Study Oversight, Communication, and Quality Checks: Since project launch, bi-weekly conference calls continue to provide oversight of all study procedures. Conference calls are led by co-PIs Dr. Matthew Siegel, Maine Medical Center, and Dr. Matthew Goodwin, Northeastern University (NU), and are attended by consultant Dr. Carla Mazefsky, RAs at the clinical study site (Spring Harbor Hospital), and members of the bioinformatics lab at NU, including James Heathers (post-doctoral fellow) and Catalina Cumpanasoiu (Ph.D. student). As reported in year 1, these call discussions provide the opportunity for reviewing and refining data collection procedures, provide RA supervision and guidance, ensure proper equipment calibration and use, and scaffold ongoing data transfer between the data collection site and the bioinformatics lab at NU - including physiological signal data collected using the biosensor and behavior coding data collected using the mobile application. These calls have evolved into a platform for discussing the quality and architecture of the data Northeastern receives, reviewing patterns observed in the data, and initial observations regarding the predictability of behaviors based on key physiological markers. * **Both sites contributed equally to oversight and ongoing communication.**

We use the REDCap (Research Electronic Data Capture) application to store participant study data including tracking participation in the physiological data collection protocol and descriptive variables regarding all sessions conducted with participants. The latter includes qualitative details collected during 'desensitization' sessions conducted with participants to help them become comfortable wearing the E4 sensor pre-data collection. We have documented any difficulty that some participants have with wearing the device and any reasons for sensor intolerance. Also tracked are the number of physiological data collection sessions conducted with each participant using the E4 and whether the signal data collected in each session is of adequate quality or involves potential equipment issues. This data is entered into REDCap for each session conducted, including session date, duration, and whether instances of aggression occurred during the session.

As described in the year one report, REDCap serves as a communication tool to alert the NU research team to new session data available for evaluation. The NU team continues to consolidate and curate the data coming in from three sources, including: (1) participant and session descriptive information from REDCap; (2) Empatica E4 sensor data accessed via the Empatica cloud; and (3) behavior data coded into the mobile application and copied to a file repository in REDCap. Using this communication/data sharing mechanism, the NU team can give the clinical site RAs rapid feedback regarding data quality. More detail regarding these ongoing data quality checks is included in the year 1 progress report. *** 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. Catalina Cumpanasoiu regularly 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: As noted in our year 1 report, protocol development, training, reliability, REDCap, and data quality procedures required more up-front time and focus than expected, leading to a delay in initiating data collection with the first tranche of participants. However, since launch, 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. 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. The first participant consented on January 9, 2019. In year 1 of this project, 14 MV-ASD children were enrolled, and physiological data were successfully collected from 8 of them. In year 2, 16 additional children enrolled, but due to the institutional halting of data collection due to COVID-19, we could complete data collection for only 2 participants. We now have institutional approval to resume data collection as of September 15, 2020, and are working on techniques to increase tolerance of wearing the device for this highly impaired population. Despite the previous pause in collecting data, all eligible admitted patients are still recruited and consented, and they can be assessed if re-admitted to the hospital.

To date, 30 children have consented for the study. Physiological data collection was attempted with 18 children thus far, and we completed 10 of these 18 children. For the 8 *attempted but not completed*, repeated desensitization sessions are being conducted with those participants who, despite repeated trials, could not successfully desensitize to wearing the E4 biosensor. This experience has provided tremendous learning for how and when to utilize the physiological data collection device best and will inform our data collection going forward.

Although unfortunate, the data collection gap due to COVID-19 has given us pause to focus on a detailed scientific examination of our data collection platform, behavior profiles we are beginning to observe in the data successfully collected, and data collection challenges to further address. We have started exploring why certain children with autism have limited tolerance for wearing the data collection biosensor, have closely studied our biosensor desensitization methods, and continue developing and recording techniques to enhance tolerance. We are also exploring our participant descriptive information to identify any phenotypic, emotional, behavioral, or cognitive profiles in children who have difficulty wearing a biosensor. We are examining strategies to accommodate the unique needs our children may have and techniques that can increase tolerance and successful use of wearable biosensors. We are currently developing a manuscript on methodological challenges and best practices for collecting wearable biosensor data from this population.

Measures and Forms: As in year 1, 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.

Note: The NU site conducted the activity described in the following Analysis Methodology section.

Development of Analysis Methodology: The group at NU has been working on classification refinement using previously collected data from pilot work preceding this award. This includes data dimensionality reduction, nonlinear models, and point-process modeling that allows for aggression prediction along different timescales. Preliminary results that we recently published (Imbiriba et al., 2020) indicate that dimensionality reduction using Principal Component Analysis (PCA) plays an important role when combined with nonlinear classification methods such as Support-Vector Machines (SVMs). Using PCA and SVM, we achieved 97% average accuracy in person dependent models (previous results were 84% accuracy) and 96% in a global model (previous results were 71% accuracy) predicting the onset of aggression in the following 3 minutes (previous results were 1 minute). This methodology also showed promising results regarding different observational intervals. When observing just 1 minute in the past but keeping the prediction for the next 1 minute, an average accuracy of 77% and 82% were obtained for person-dependent and global models, respectively. Although these results show relatively inferior performance with respect to the SVM+PCA results discussed above, they are in the same range of results obtained in our previous study. We also performed experiments increasing the prediction interval range from 1 to 1.5 and 2 minutes for different past observational intervals (1 and 1.5 minutes). For these experiments, we obtained an average performance of 89%-90% (person-dependent–global) and 77%-82% (person-dependent – global) for 1.5 and 2 minutes, respectively. Although such results are promising, it is essential to highlight that the limited amount of data analyzed thus far limits the observational intervals' extension and generalization of results. More thorough experiments using the more extensive data set being collected in Maine will enable us to evaluate this new methodology and explore prediction accuracy at increasingly longer time scales in the next year of the project.

Another probabilistic methodology we are exploring is non-homogeneous Poisson processes (NPP) by considering data-dependent intensity functions. This approach has several advantages over standard classification methods, such as those we have explored up to this point in the project. Among these advantages are: (1) provides a probability measure for the onset of aggression; (2) allows prediction at extended time scales; and (3) provides an expected number of aggression episodes for a given time interval. In NPP models, a primary challenge is accurately estimating parameters of the intensity function. Several models and estimation techniques can be applied to this task, including linear and nonlinear (shallow and deep) models optimized by least-squares (LS) and maximum likelihood estimation (MLE). Up to this point in the project, linear and kernel-based nonlinear models have been explored, providing results that agree with the ones provided by their respective counterparts explored in the previous studies (i.e., logistic regression and SVM). Specifically, observing 3 minutes in the past and predicting the onset of aggression in the next minute, we obtained average performances (currently only for the person-dependent model) of 79% and 78% for the linear intensity model with LS and MLE, respectively, and 97% for the kernel-based intensity function using epsilon-intensive support vector regression (SVR). We are still in the process of developing these multiscale learning and prediction methodologies.

Beyond continuing to develop the above NPP models and algorithms, our short-term Y2 objectives are to (1) verify the independent replicability of PCA+SVM in the newly acquired 71 data collection sessions from 8 participants and (2) assess preliminary results extending our prediction interval up to 10 minutes using a data set that combines both our previously collected and recently collected participants.

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 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, developing a protocol for observational timestamped coding of aggression, and measuring physiological arousal using validated wrist

worn biosensor technology. Through preliminary testing, we established the incipient feasibility of our research protocol. We demonstrated in 20 MV-ASD patients over 69 independent observational sessions that all combined biosensor data can predict the onset of aggression on average 1 minute before it occurs with 71%- 84% accuracy, depending on whether global or person-dependent prediction models are used.

As described in our proposal and year 1 report, we now 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 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 a combination of two factors: the pre-data collection time (in year one) required to ensure aggression coding inter-rater reliability and implementation of our data tracking and quality assurance mechanisms, and the significant impact of COVID-19 (in year two) on our ability to complete hands-on data collection with children admitted to the hospital unit since March 2020. However, we have consented 30 children and finished data collection with 10 of them.

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.

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. We are resuming active data collection in September 2020, now that we are allowed to collect data by our institution.

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.

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?
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 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?
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.

With sophisticated data collection, reliability, and physiological data quality assurance strategies in place, we will continue to recruit, enroll, and conduct data collection with MV-ASD youth admitted to the inpatient unit at Spring Harbor Hospital. Despite the COVID-19 related pause in data collection sessions, we continue to consent and enroll admitted patients through local face-to-face contact. We will restart data collection in September 2020, with a significantly greater frequency of data collection sessions to catch up to our target enrollment. We will complete data collection sessions with children consented during the pause and readmission to the hospital. Finally, we will stay the course, conducting additional desensitization sessions with children with low tolerance for the device, utilizing all strategies at our disposal. We will seek to determine why (defining features, behavior profiles, physiological signals) some children have difficulty with the biosensor and hope to contribute these insights to the field, for families, caregivers, providers, and researchers regarding how to utilize best this biosensor paradigm for prediction, prevention, and real-time intervention for children with the most severe behavior challenges.

IMPACT
D*escribe 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).

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 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 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?

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.*

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:
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.

No significant changes in approach have been made in the past year.

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.

Two problems have occurred. As described previously, our enrollment and data collection completion is lower than expected due to a delay in our launch of physiological data collection and an institutionally mandated pause in data collection from March to September 2020 due to the COVID-19 pandemic. However, 30 children have consented to the study, 10 participants completed data collection, and another 13 have consented and are eligible for data collection should they return for readmission to the hospital. We restarted data collection in September 2020. We anticipate requesting a no-cost extension at the end of the study period, which will help us reach our enrollment and data collection targets. The second problem observed was the difficulty some children have tolerating wearing the E4 biosensor. Eight of the 18 minimally verbal children who participated in repeated desensitization sessions could not adjust to wearing the sensor on their wrist, despite repeated efforts, the use of supportive techniques (sports band, sleeve coverage, proper fit adjustment), support from clinical staff, and various other strategies (distraction, reward/reinforcement for wearing the device, etc.). We are now closely examining why these children had difficulty and exploring further plans to enhance their tolerance.

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. Maine Medical Center IRB continuing review approval was granted on 6/17/2020, expiration date is 6/14/2021. Human participants are not enrolled at NU, and thus no IRB approval is required.

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".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name:	*Matthew Siegel, MD*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1.0 Calendar Month*
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:	*Jocelyn Ng*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*4.5 Calendar Months*
Contribution to Project:	*Assisted in enrollment, consent, and data collection with participants; data entry and physiological data upload to NU site.*
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, 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.