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TITLE: iANAM: The Ability to "Visualize" Headache, Sleep Disturbance, and mTBI

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14. ABSTRACT The purpose of this research was to integrate simultaneously collected eye movement data with computerized cognitive assessment data (ANAM) for improved clinical management of mTBI. Not having access to ANAM application programming interface (API), and identification of ANAM timing irregularities, has required adapting proposed eye movement metrics. It has also required greater development emphasis on the eye-tracking platform (Gazepoint) generally adapting to the ANAM platform, which cannot be modified.		

15. SUBJECT TERMS Eye-tracking, fixations, saccades, scan path, pupillometry, Automated Neuropsychological Assessment Metrics (ANAM), computer based cognitive assessment, mTBI, headache, pain, sleep disturbance, insomnia, sleepiness, multimodal data					
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1. INTRODUCTION:

The purpose of this research was to integrate simultaneously collected eye movement data with computerized cognitive assessment data (ANAM) for improved clinical management of mTBI. Not having access to ANAM application programming interface (API), and identification of ANAM timing irregularities, has required adapting proposed eye movement metrics. It has also required greater development emphasis on the eye-tracking platform (Gazepoint) adapting to the ANAM platform, which cannot be modified.

2. KEYWORDS:

Eye-tracking, fixations, saccades, scan path, pupillometry, Automated Neuropsychological Assessment Metrics (ANAM), computer based cognitive assessment, mTBI, headache, pain, sleep disturbance, insomnia, sleepiness, multimodal data

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: The primary aim of the proposed project is to use the eye-tracking parameters of fixations, saccades, and scan path (combination of fixations and saccades to complete a specific task) fully integrated with the ANAM Military battery to improve the sensitivity of mTBI detection and resolution.

Specific Aim 2: The secondary aim is to use the eye-tracking parameter of pupil dilation fully integrated with the ANAM Military battery to provide greater specificity (or differentiation from mTBI) of state dependent influences (i.e., sleep disturbance, headache, mood, engagement/effort) of impaired post-traumatic cognitive performances compared to current clinical decision making.

Major Task 1: Finalize Protocols and Obtain IRB Approval

- Subtask 1: PI and Co-I create written protocol and obtain institutional IRB approval
- Subtask 2: Submit HRPO documentation
- Milestone #1: *HRPO approval obtained*
- Subtask 3: Two teleconference meetings of all key personnel to review study protocols and technical build metrics
- Milestone #2: *Initial build metrics finalized and establish regular meetings (AV will participate as needed through Milestone #3)*

Major Task 2: Integration and Synchronization of ANAM & Eye-Tracking Modalities (iANAM)

- Subtask 1: Establish hardware configuration and calibration of GP3 eye-tracker, CPU specifications, and desktop screen
- Subtask 2: Establish eye-tracking metrics: sampling rate, head box, fixation, saccadic, scan path, and pupillometry operationalization using eye-tracker SDK, ANAM xml output, timestamps, etc.

Major Task 3: iANAM Pilot Testing

- Subtask 1: Recruit pilot testing volunteers; [10 clinical + 10 control volunteers]

- Subtask 2: Assess calibration and data quality of iANAM; modify software and hardware as necessary
- Subtask 3: Assess pilot testing volunteers' reaction/satisfaction of iANAM
- Milestone #3: *iANAM ready to launch*
- Milestone #4: *Write and submit for publication results from iANAM pilot testing*

Major Task 4: Conduct Pilot Comparison Study of iANAM Military Battery and ANAM Military Battery regarding mTBI detection and resolution.

- Subtask 1: Recruit study subjects
- Subtask 2: Conduct pilot comparison study; [35 mTBI subjects and 35 control subjects]
- Milestone #5: *Two meetings of all personnel to discuss database, analyses, and outcome interpretation*
- Milestone #6: *Write and submit for publication results from iANAM versus ANAM comparison pilot testing*

What was accomplished under these goals?

1) Major activities for Task 1:

- a. Institutional IRB approval and HRPO approval obtained
 - i. Required reliance agreement following meeting of scientific officer and OHSU IRB officials
 - ii. All subject recruitment moved to OHSU (previously controls recruited at UNT)
 - iii. Revised SOW and budgets for OHSU and UNT submitted – only consultant retained was Andrea Vincent due to budget revisions
 - iv. FITBIR initial training complete, and project application accepted
 - v. OHSU Department of Family Medicine clinical leadership team approved research request to recruit clinical patients for research participation.
- b. Graduate research assistant (experimental psychology PhD candidate) with eye-tracking experience hired at UNT (Co-I's lab)
- c. Teleconferences held with training on ANAM (computerized cognitive battery software) and protocols
- d. Weekly meetings established
- e. Software and hardware obtained and configured
 - i. Three month administrative delay in UNT acquisition of equipment

2) Major activities for Task 2:

- a. Software calibration completed and calibration protocol established
- b. Test data collected and analyzed to establish protocol
 - i. Document created and regularly revised: "Procedures for collecting data"
- c. Timing and communication between eye-tracking software (Gazepoint) and ANAM software tested
- d. Document created: "Codebook for Gazepoint"
- e. Procedures established and tested for accessing ANAM data
- f. Procedures developed for data processing via Area of Interest (AOI) creation for the ANAM subtests: Matching to Sample (M2S), Simple Reaction Time (SRT), and Code Substitution (CDS)
 - i. Prioritized M2S (completed), then SRT (will finalize AOIs after pilot recruitment, see "other achievement" section below for explanation), and will

- continue development of CDS after finalizing SRT AOIs following pilot recruitment and expected beta development refinement
 - ii. See the document “After running the macro creator” for AOI development status details for SRT and CDS
 - g. All AOI boundaries established
 - i. Document created: “Creating AOIs for M2S manually”
 - h. Data processing was time extensive. A macro was coded to automate AOI creation
 - i. Document created: “Instructions for running the AOI macro”
 - ii. Document created: “After running the macro creator”
 - iii. Document created: “Edit or understand the AOI automation for M2S”
 - iv. Document created: “Using Pullover’s macro creator”
 - i. Eye-tracking metrics established
 - i. Document created: “Pupillometry in SRT”
 - ii. Document created: “Lit Review 11.1.21”
 - j. AOI creation automation for alternate forms of the matching to sample (M2S) task begun (50% complete)
- 3) Major activities for Task 3:
 - a. Clinical and Control Recruitment Fliers created and approved by OHSU communications department, then by OHSU IRB
 - b. Fliers placed in several locations at the PI’s medical clinic and the lobby TV screen
 - c. ClinCard account created, approved, and debit cards received as of 4/2022. ClinCard is the OHSU approved payment method for study participants. ClinCard payments are processed using re-loadable debit cards through an electronic payment system.
 - d. Adding required ClinCard language to informed consent approved by OHSU IRB.
 - e. Hardware configuration testing:
 - i. Purchased dual monitor desk stand for uniform hardware configuration (i.e., monitor, mounted eye-tracker, keyboard, and mouse). The height of the monitor (and mounted eye-tracker) and the height of the shelf holding the keyboard/monitor can be adjusted in uniform manner to match participant height and testing taking comfort preferences.
 - ii. Dual monitor configuration recommended by gazeport so analysis software can be monitored by researcher during data collection on separate screen from the screen research participants are using to complete the ANAM battery. Trial and error monitor configurations and display settings (ie, extended or duplicated) were not able to overcome the ANAM software blocking (blue screen) screens that ANAM test battery is not being presented on in multiple monitor configurations. Thus, Gazepoint software is simply running in the background during completion of the ANAM test unable to be actively monitored by researchers for real time assessment of eye movement data quality (e.g., need of recalibration during testing).
 - iii. Purchased single monitor desk stand (same brand and general configuration as dual monitor) and configured with all hardware.
 - iv. Purchased a commercial academic classroom chair that has the ability to adjust height (so can compensate for variability in height of respondents) in addition to ability to adjust desk stand monitor and keyboard shelf height, but is not a wheeled chair that can swivel to minimize eye-tracking movement related error.

- v. Have completed full data collection procedures with two graduate students to assess hardware configuration efficacy to reduce potential that data collection methodology as source of error related to software integration and prior to paid pilot research participants.
 - f. PI completed required OHSU REDCap basics training prior to approval of database build. UNT collaborators added to OHSU REDCap. Completed initial meeting with REDCap informaticist (an institution research service through the Oregon Clinical and Translational Research Institute, or OCTRI) regarding best practices for data sharing given volume of data created from Gazepoint and ANAM software to be sent from OHSU to UNT for analysis. Informaticist recommended using of Microsoft Teams for data sharing of deidentified data between institutions for analysis, to then be collated and stored in REDCap. Participant screening, informed consent, scheduling, and collection of demographic data also being completed in REDCap database.
 - g. PI will be meeting with OHSU marketing and Epic (electronic medical record) personnel (following the submission of this report, likely sometime in the end of April or beginning of May) as coordinated via the OCTRI informaticist meetings to optimize participant recruitment via public forums (e.g., OHSU websites) and automated inclusion criteria identification in the electronic medical record based upon scheduled visit information.
- 4) Specific objectives:
- a. Institutional IRB approval and HRPO approval obtained
 - b. Two teleconference meetings of all key personnel to review study protocols and technical build metrics
 - c. Weekly development meetings with graduate research assistant and PI, Co-I attends when available
 - d. Initial AOI build metrics finalized for ANAM SRT & M2S subtests (two subtests shown to be most sensitive to concussion and concussion recovery)
 - e. Establish hardware configuration and calibration of GP3 eye-tracker, CPU specifications, and desktop screen
 - f. Establish eye-tracking metrics: sampling rate, head box, fixation, saccadic, scan path, and pupillometry operationalization using eye-tracker SDK, ANAM xml output, timestamps, etc.
 - g. Begin pilot data collection for ongoing refinement of development pipeline
- 5) Significant results or key outcomes:
- a. We noticed that the timing of responses using ANAM software was variably inaccurate by a few milliseconds during subtest events. Timing inaccuracies did not appear consistent both within subtest administrations and across subtests, which we were unable to be confirm as subtests events are not individually time stamped in the desktop version on ANAM (as well as not having access to ANAM API as previously noted). Given that eye-tracking requires millisecond level resolution, latency (timing) discrepancies between the eye-tracking system and ANAM timing inaccuracies introduces additional error and presents a barrier to integrated eye-movement and cognitive performance data. Less time-based eye-movement metrics (e.g., saccadic latency) were emphasized during development as such, and adapted to AOI emphasis (leveraging more spatial based eye movement variables).
 - b. Data processing was slow so the process was automated (see major activity m. above).

- c. Pilot data collection is ready to begin
- 6) Other achievements:
 - a. Data processing automation was created using a script-based macro. One was created to specifically investigate one form of the matching to sample (M2S) task and another version is being created to use on any M2S task, as well as the SRT task. The SRT macro is partially completed and will be finalized based on average fixation distances (from AOI around stimulus on the center of the screen) of pilot participants. The graduate student thus far has found the average distance away from the stimulus center of all gazes during SRT (on data collected on herself) and make an AOI with that average distance as the radius, it will be quite small (smaller than the stimulus itself) and 76.6% of gazes will fall inside of it. If an AOI is made that is double the diameter, 93.4% of the task time was spent in that, and the third AOI did not add much. We also learned that the height of AOIs in gazepoint equal to 16/9 times the width are perfect circles, which is preferable for data analysis.
 - b. Eye-tracker calibration related to pupillometry variables:
 - i. After extended troubleshooting, we discovered how to export csv files from gazepoint for Blink rate, Blink duration, Pupil diameter, in addition to other fixation and saccadic data points
 - ii. We also found that eye-tracker calibration (e.g., pupil diameter measurements) was greatly enhanced by a calibration of the inter-pupil distance (IPD) by imaging a gazepoint marker of known size during calibration, which compensates for not having a chinrest (ideal for pupillometry but not conducive for goal of remote administration of iANAM following the current initial validation). The marker is printed on printer paper with an adhesive side and affixed to the forehead between the eyes. During calibration press 'm' to confirm the marker has been identified (outlined in red). Redo calibration as normal and the IPD should be calculated. Please see attached page on Gazepoint Control IPD Calibration.
 - iii. Other considerations: keeping hardware configuration and participant configuration to hardware as standardized and stationary as possible (see "Major Activities for Task 3" section e. above)

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

The project was not intended for training, but the PI has been learning eye-tracking theory and practice via development activities with the graduate student with eye-tracking experience, as well as reading eye-tracking textbooks to support development activities.

How were the results disseminated to communities of interest?

Nothing to report.

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

- 1) Co-I will be hiring a computer science graduate student to extend current development of automation procedures (i.e., macros). Our concern is how to best deal with latency

discrepancies between the ANAM and Gazepoint software discussed above. In addition to macros, we are considering purchasing screen capture software (in addition to gazepoint functionality), developing automation software that would use macro gazepoint coordinates that have been established for automated processing, but overcoming macro limitations (e.g., processing each ANAM subtest eye-tracking data uniformly and sequentially versus separate macros for each subtest). Possibly switching to a single core processor, running the software simultaneously on separate computers, but cloning the monitors is also being considered as possible solution to potential ongoing latency issues following pilot data collection.

- 2) Acquire REDCap database build approval for production, likely will occur in 4/2022. A second meeting with the REDCap informaticist is scheduled for 4/14/2022 to review recommended build configuration.
- 3) Begin collecting paid pilot research participants.
- 4) Process all pilot data. This will be done by first using the automated AOI creation procedure as well as manual adjustments for accurate timing to process eye-tracking data. Eye-tracking data will then be exported. ANAM data will be exported and combined with eye-tracking data. Data will be checked for irregularities, frequency of blinks/off-screen looks/missing data. Eye-tracking coordinates will be converted to a standard metric in both directions (eye-tracking output coordinates are relative to screen width and height, meaning horizontal and vertical distances cannot be compared without first being converted). Average distance from stimulus and from center screen will be calculated for the simple reaction time (SRT) task. That will be converted back to screen coordinates to create standard AOI size for SRT task for study participants.
- 5) After beta development of SRT and CDS AOIs following pilot testing, the development team will begin to examine pupillometry metrics related to *Specific Aim 2* in conjunction with actively recruiting research participants.
- 6) Data will be analyzed by comparing the control and mTBI groups on eye-tracking metrics (i.e., fixation, saccadic, scan path, and pupillometry metrics) and ANAM performance. This will be done across several tasks included in the ANAM Military Battery. The goal is to determine if using both eye-tracking metrics and ANAM data improves the ability to distinguish mTBI and control participants. This step will also help determine if procedures need to be adjusted in order to collect better data from the study participants.
- 7) Collect study data from 35 control participants and 35 mTBI participants.
- 8) All study data will be processed in a similar manner to processing for pilot data. AOI creation will be automated where appropriate (i.e., for the M2S task). Eye-tracking data will be exported and combined with exported ANAM data. Standards developed based on previous research and pilot testing will be used for SRT AOI size and acceptable missing data percentage. Data will be stored securely and shared with collaborators via REDCap and Microsoft Teams.
- 9) Run statistical analyses.
- 10) Write manuscript detailing results.
- 11) Submit manuscript for publication.

4. IMPACT:

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

Nothing to report.

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?

Nothing to report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

- As noted above due to required IRB reliance agreement, control participants initially proposed to be recruited at UNT was modified to all participant recruitment (clinical and control participants) to be recruited at OHSU.
- As noted above due to ANAM timing inaccuracies and then associated eye-tracking & computerized cognitive test latency issues, adapted to more spatially based versus timing - based variables. Specifically, procedures developed for data processing via Area of Interest (AOI) creation.
- Changed from the ANAM Military battery (specific to mTBI) to the ANAM Core Expanded battery following initial meetings with Dr. Vincent. The batteries are essentially the same, but the military battery has demographic questions specific to military personnel as well as a military version of the PTSD screener (PCL) that would not be relevant/appropriate for the proposed civilian participant sample.

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

- As noted above, administrative delays in sub-contractor access to funds resulted in not purchasing hardware/software until 3 months from the start of the grant, which resulted in delay in coordinated development activities.
- The reliability of pupillometry during sequential and dynamic stimulus presentation (i.e., a battery of individual computerized cognitive tests) is a concern for the graduate assistant with eye-tracking experience, and may result in an invalid iANAM integrated variable regarding pupillometry. See “other achievements” section b. above for the proposed resolution during development that will be clarified during analysis.
- Proposed resolution would be a Year 3 no cost extension to the performance period.

Changes that had a significant impact on expenditures

Nothing to report.

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

Nothing to report.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Nothing to report.

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**

AOI script-based macro development for the ANAM subtests M2S, SRT, and CDS as described above

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

(a person month equals approximately 160 hours of effort).

<i>Name:</i>	Tyler Duffield
<i>Project Role:</i>	PI
<i>Nearest person month worked:</i>	2.41
<i>Contribution to Project:</i>	Grant writer, literature reviewer, iANAM variable development, iANAM hardware configuration development, IRB development and approval, ClinCard approval and activation, REDCap development and activation, (unofficial or unpaid) pilot subject recruitment and data collection.

<i>Name:</i>	Megan Kelly
<i>Project Role:</i>	Graduate Research Assistant
<i>Nearest person month worked:</i>	1.125 (Time worked on this grant is in-kind.)
<i>Contribution to Project:</i>	iANAM variable development, script-based macro development, REDCap development, processing of (unofficial or unpaid) pilot data.

<i>Name:</i>	Thomas Parsons
<i>Project Role:</i>	Co-I
<i>Nearest person month worked:</i>	2.41
<i>Contribution to Project:</i>	Supervising graduate research assistant development activities at the University of North Texas (UNT).

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?

Organization Name: University of North Texas

Location of Organization: Denton, Texas

Partner's contribution to the project:

- *In-kind support:* Primary site for iANAM development activities
- *Facilities:* Graduate research assistant was hired at UNT and works in Co-I's research laboratory
- *Collaboration:* Collaborative development activities, collaborative analysis activities once participant recruitment commences, and future collaborative production of scholarly materials from data generated from the grant

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Not applicable.

QUAD CHARTS: Not applicable.

- 9. APPENDICES:** Please see "Other" attachment for combined pdf of all referenced documents created under this award.