Using Machine Learning to Explore Multimodal Digital Markers for Early Detection of Cognitive Impairment in Alzheimer's Disease

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BACKGROUND

Recent technological advancements have revolutionized our approach to healthcare, enabling us to harness the potential of smartphones and wearables to collect data that can be used to characterize Alzheimer's disease (AD) heterogeneity and develop digital biomarkers. Our focus is on creating comprehensive cross-domain digital datasets that can inform on the emergence of cognitive impairment.
Central to accelerating the potential of digital biomarkers for more accurate and early detection is privacy-protecting data access. When combined with deep molecular phenotyping, this approach enhances our understanding of the biological mechanisms underlying clinical expression. This emerging project aims to use clinical digital biomarkers to predict the onset of cognitive impairment, focusing on sleep data and response time as key digital markers.

Two specific tasks being highlighted in this study are the **Code Substitution Task** and the **Go-No-Go Task**:

1. **Code Substitution (CS) Task**:

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1	2	3	4	5	6	7	8	9

This task assesses measures of working memory, involving frontoparietal and cortical function. Participants must match symbol-digit pairs to a code set of nine symbol-digit pairs by selecting "yes" or "no" within a time limit. It is sensitive to changes in processing speed, attention, and working memory.

❀
8

Match?
Yes or No

2. **Go-No-Go Task (GNG)**: This task assesses response inhibition and executive control by having participants respond to certain stimuli (Go) and withhold responses to others (No-Go). Performance on this task can reflect the integrity of frontal lobe functions, which are often affected early in the course of AD.

= foe = friend

Differentiate between "foe" and "friend" stimuli and press a button as quickly as possible when the foe appears

X	X	X
X	☻	X

By integrating data from these tasks with other digital biomarkers, we aim to create a robust predictive model for early cognitive impairment, ultimately leading to earlier and more accurate detection of AD.

METHODS

DATASET:

Ongoing project from the Boston University Alzheimer's Disease Research Center, gathering continuous data from subjects to identify predictive digital biomarkers of cognitive impairment.

Preliminary Phase
n=64 subjects
n=1450 variables involving sleep-derived variables

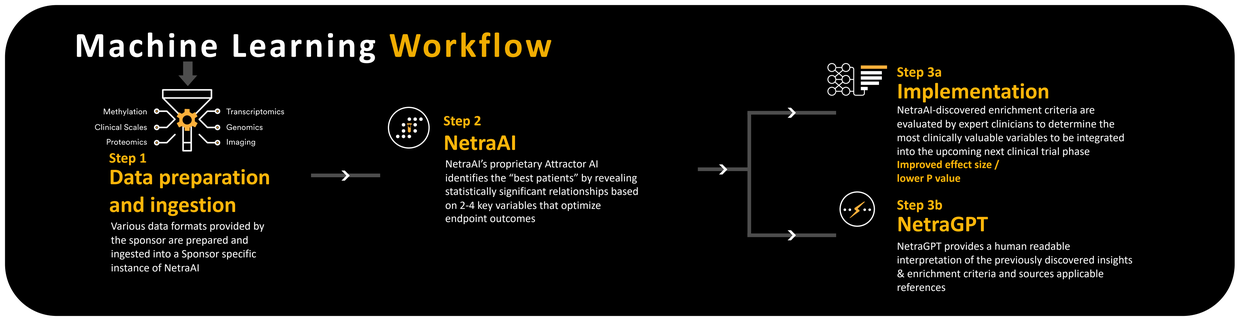
Secondary Phase
n=109 subjects
n=636 variables covering Code Substitution and Go-No-Go Tasks

MACHINE LEARNING APPROACH:

Our analysis approach leverages a novel machine learning (ML) technology, NetraAI, powered by its unique Attractor AI algorithms, that is capable of differentiating causal and non-causal subpopulations within small patient or study populations and large volumes of measures that can enhance the efficacy of predictive models.

Attractor AI:

- Fractures small patient populations into causal and non-causal subpopulations that capture different aspects of complex disease states
- Powerful tool for building predictive models as it allows the resulting biomarker to run "No Calls" for samples that do not correspond to the causal subpopulations.



RESULTS

Sleep-Derived Variables Characterizing Cognitive Impairment

Using the preliminary dataset (n=64), NetraAI was able to characterize 50% of the 27 cognitively impaired (CI) subjects.

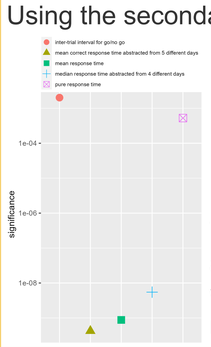
A subpopulation of 8 subjects (7/8 being CI) characterized by higher sleep-derived variables including:

- 3% desaturation threshold ($p=4x10^{-5}$)
- 4% desaturation threshold ($p=7x10^{-5}$)
- Periodicity (eLFCnb) ($p=0.008$)

Incorporating maximum heart rate captures another group of 8 subjects (6/8 being CI) distinguished by elevated heart rate during one or more of their measuring instances ($p=10^{-10}$)

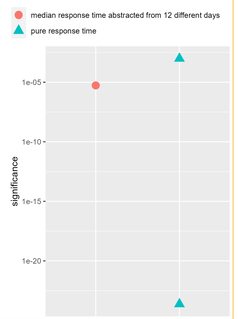
Cognitive Task Variables Characterizing Cognitive Impairment

Using the secondary phase data, we used NetraAI to identify subpopulations that characterized subsets of CI transitioners.



27/109 subjects were explained with respect to CI transitioning. (12/27 transitioners, 75% accuracy; and 15/27 non-transitioners, 80% accuracy) characterized by the significant values of 11 CS events and 1 GNG event. Lower scores favored non-transitioners across all variables.

32/109 subjects were explained with respect to CI transitioning. (9/12 non-transitioners, 75% accuracy; and 15/20 transitioners, 75% accuracy) characterized by the significant values of 12 CS events. Lower scores favored non-transitioners across all variables with pure response time for CS ($p=2.35x10^{-24}$)



These items can be used to produce a digital biomarker for the prediction of individuals who are at risk for transitioning into CI. The model will utilize NetraAI's ability to accurately decide when it cannot make a decision about people that do not fit into the described sub-insight model.

CONCLUSIONS & SIGNIFICANCE

CONCLUSIONS:

The findings of this study to-date highlight the role of several aspects that characterize the transition to cognitive impairment:

- Preliminary higher sleep-derived variables coupled with elevated maximum heart rate characterize subpopulations of CI.
- Cognitive tasks including Code Substitution and Go-No-Go data were used to differentiate CI transitioners versus non-transitioners, with lower scores favoring non-transitioners.

These findings highlight the heterogeneity and complex interactions that take place during the transition to cognitive impairment that can be used as biomarkers to help with the diagnosis, treatment, or prevention of the potential transition to AD.

SIGNFICANCE:

While these results are preliminary, they signal a promising direction to integrate diverse data in order to expose a more accurate understanding of the emergence of cognitive impairment. This can lead to an understanding of AD risk pathways that might be amenable to early intervention and delay. Future studies will focus on integrating further modalities of data derived from digital sources.

CONCLUSION:

The next steps for this project include expanding the scope of multimodal digital data to encompass aspects like vocalizations and speech patterns derived from self-administered picture description and picture description recall cognitive assessments, and features from gait analysis, physical activity, and other cognitive tests and games.

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