Episodic Memory Trajectories as Preclinical Indicators of Alzheimer's Disease and Spatial Navigation Deficits

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Posted Date: 28 June 2024

doi: 10.20944/preprints202406.1984.v1

Keywords: Alzheimer's disease, Preclinical, Tau, Amyloid, Navigation, Memory

 doi:10.20944/preprints202406.1984.v1

Article

Episodic Memory Trajectories as Preclinical Indicators of Alzheimer's Disease and Spatial Navigation Deficits

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Abstract: Introduction: It may be feasible to detect episodic memory change in preclinical Alzheimer's disease (AD) to indicate navigational risks and AD prior to mild cognitive impairment. The establishment of episodic memory signatures may allow for biomarker mapping to inform diagnostic research and practice. **Methods:** Retrospective longitudinal mixed methods and cross-sectional effect size, to compare group differences, are applied to the Craft-21 memory scores from the preclinical years of persons who later developed AD (pre-AD) dementia , n = 175 with 112 females and 63 males. Their scores are compared to cognitively normal controls (non-AD) n = 6,814 with 4,232 females and 2,582 males. Pre-AD and non-AD groups are further analyzed by biological sex. The dataset is from the National Alzheimer's Coordinating Center funded by NIA/NIH Grant U24 AG072122. **Results**: The pre-AD episodic memory scores decreased an average of -.510, p < .001 versus (vs.) the non-AD annual increase by .127, p < .001. The first Cohen's d = .482 and last Cohen's d = 976, p < .001. The pre-AD females had an average annual decreased of -.762, p < .001 vs. non-AD females increase of .117, p < .001. The first Cohen's d = .576 and last Cohen's d = 1.133, p <.001. The pre-AD males increased every year by .185, p = .996 vs. the non-AD males annual increase of .185, p < .001. The first Cohen's d = 1.054 decreased by the last year to Cohen's d = .680, p <.001. **Discussion:** Distinct decline in episodic memory occurs for pre-AD females, but there is not a significant change in pre-AD males. However, the effect size difference between both pre-AD and non-AD groups suggests biomarker mapping in conjunction with memory trajectories may be feasible to determine potential navigational risks as well as biological and cognitive preclinical AD.

Keywords: Alzheimer's disease; preclinical; Tau; amyloid; navigation; memory

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Despite many decades of research, there is not a cure for Alzheimer's disease (AD) [1,2]. By the time of diagnosis, the pathology has spread throughout the brain resulting in profound losses in episodic memory and spatial navigational (SN) ability [3,4]. Severe impairments appear in common SN abilities such as orienting oneself within an environment and following a route and developing a cognitive map of a journey [5,6]. Deterioration in episodic memory diminishes the ability to retrace traveled routes, recall journey landmark, as well as remember the present location of self in the environment [7]. Damage to the areas of the brain involved with these abilities and memory begins during the preclinical stage when persons are cognitively unimpaired [8]. Thus effective preclinical interventions are highly desirable, but detecting the disease when persons are cognitively intact is not yet an option for clinical practice [9]. However, due to the locations of the early pathology in the brain [8], it may be possible to detect subclinical changes in episodic memory and SN [10,11].

Over the span of the 20-to-30-year preclinical time frame, amyloid plaques develop in the frontal cortex [8,9] that is involved with the retrieval of episodic memory and executive functions to inform SN related judgement while navigating a route [10]. Inside the entorhinal cortex, tau-related damage neuronal damage from neurofibrillary tangles (NFTs) [8] develops (see Figure 1) where there are SN-related cells, grid and time cells, that inform SN and episodic memory [7,12,13]. Furthermore the neuronal damage may impair signaling for episodic memory and SN functions in the hippocampus where SN place cells are demonstrated to be active in measurements of episodic verbal recall [14]. Although, the standardization of preclinical biomarker levels of amyloid and tau still remain a matter of research [9], it may be possible to measure biomarker levels along a longitudinal trajectory of

 doi:10.20944/preprints202406.1984.v1

verbal episodic memory change. This might increase the likelihood of early AD detection and enable assessment of patients for any changes in memory related to SN tasks such as recall of routes, or behavior changes such as depression altering their driving ability. If so, then interventions may be designed to treat the changes in these functions. The result may decrease losses in memory, spatial navigation ability, and societal impact of the disease. In order to establish a possible trajectory of episodic memory change to map preclinical biomarkers, a retrospective secondary longitudinal analysis was performed on verbal episodic memory during the cognitively normal years in a sample that was later diagnosed with AD (pre-AD). This analysis may reveal a clinical indicator of this stage if the pre-AD sample scores are different from their contemporaries who did not go on to develop the disease. The Craft 21 neuropsychiatric test of episodic memory requires a person to recall a short story verbally [15]. Although the narrative features several story elements, one is navigation, it is not considered a measure of SN memory. The test is 1 of 22 stories Dr. S. Craft and colleagues created. Of all the stories, it was considered the most general in applicability as for reliability and validity in measuring verbal episodic memory [16].

This paper reports the findings from the (a) comparison of longitudinal Craft 21 scores of pre-AD and non-AD persons and (b) changes in scores for females and males to determine the feasibility of this measure as cognitive indicator of preclinical AD (stage 1a and 2b) and SN changes.

Methods Data Sources

Participant data for this retrospective longitudinal study was obtained from the National Alzheimer's Coordination Center (NACC) Uniform Data Set (UDS). The ADRCs and NACC follow ethical protocols and standards in all aspects of participant and co-participant data collection and the maintenance of the deidentified participant data in the UDS [16]. The ADRCs obtain participant and co-participant consent per approval by individual Institutional Review Boards (IRBs). The data is further reviewed by IRB at University of Washington prior to public availability for researchers. Therefore, the secondary analysis of the data was exempt from IRB approval as confirmed by Washington State University. The data is publicly available for research. The data retrieved for this study are from the September 2022 NACC dataset freeze.

Sample

A longitudinal sample of pre-AD participants that received annual testing with Craft 21 when they were cognitively normal were selected from the dataset. There was a range of 1 to 6 years of participant assessment data for analysis (see Table 1). The total sample was n = 175, with 112 females and 63 males. The number of non-AD participants tested with Craft 21 was 6,826, but 12 were removed for having an age outside the range of the pre-AD group; thus, the non-AD sample for analysis was n = 6,814 with 4,232 females and 2,582 males. None of the participants in each group were positive for autosomal dominant AD. The non-AD sample data was collected from all the ADRCs whereas the available pre-AD sample was from 20 ADRCs.

Cognitive Assessment Data

The neuropsychiatric test battery includes multiple tests to measure cognitive domains, but none of the tests are a direct measure of SN. The participants are screened for dementia with the Clinical Dementia Rating (CDR) scale. All participants receive a score of 0 if they are considered cognitively normal. Early impairment is given a CDR= 0.5; an increase in mild impairment is CDR=1; moderate impairment is CDR=2, and severe impairment is CDR=3 [17]. The cognitive test results are contextualized with the participant health history and current physical assessment data.

The NIA ADRC protocol for clinicians to administer the Craft 21test requires them to read the story aloud to the participant. Then participant must repeat the story to the clinician immediately after hearing it, and then 20 minutes later, they repeat what they recall of the story. For the paraphrase scoring of the story, there is maximum of 25 points. A high score indicates better memory than a lower score.

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Statistical Analysis

To address the study aim, linear mixed effects were applied. It is considered an adaptive analysis for longitudinal studies that may have varying sample sizes and missing visit data points [18]. The analysis applies fixed effects for the groups over time, random effects for the time, and individual differences. Cohen's *d* represents the equivalent of Glass's delta, a measure of effect size, for unequal sample sizes and is applied to specific time points when the confidence intervals (CI) do not overlap.

Results

The pre-AD group average score decreased every year by -.510, $p < .001$, and CI (-.757, -.264). The non-AD group average score increased by .127, $p < .001$, and CI (.101, .153). The effect size after the CIs did not overlap was Cohen $d = .482$ and the last visit Cohen $d = .976$, $p < .001$ (See Figure 2).

The pre-AD female group average score decreased every year by -.762, $p < .001$, and CI (-1.059, -.464). The non-AD females average point increased each year by .117, $p < .001$ and CI (.085, .148). The effect size after the last CI overlap was Cohen's $d = .576$ and by the last visit

The pre-AD male group average score increased every year by .185 but this was not significant $p = .996$ with and CI (-.453, .451). However, the non-AD males' average score increased by 185 but this was not significant $p = .996$ and CI (.138, .232). The effect size after the last confidence interval overlap was Cohen's $d = 1.054$ and decreased by the last visit to Cohen's $d = .680$ and $p<.001$ (Figure 4).

Discussion

This study compared longitudinal verbal episodic memory scores over time in the cognitively normal years (Stage 1a and 2b) of pre-AD persons and those who remained cognitively healthy. Males and females were also compared. The pre-AD group and the females from this group demonstrated a significant decline in scores over time compared to those who did not progress to AD. Although pre-AD males increased in scores as they advanced to an eventual diagnosis, the results were insignificant despite the medium effect size by their last visit as normal. The pre-AD group had four years remaining as cognitively normal and the pre-AD females had 3 years remaining as cognitively normal without any overlap in the CIs.

Current literature suggests women outperform men on episodic memory [19,20]. In both cross-sectional and longitudinal studies, there are minimal differences in episodic memory among the cognitively normal persons with and without AD biomarkers [21–24]. The past preclinical studies on episodic memory were predictive models with persons who had AD biomarkers, but it was unknown whether they would progress to AD dementia. However, this study definitively identified that persons who progress to AD dementia will have statistically significant declines in episodic memory at least 4 years prior to the end of the preclinical stage. This is when the tau related NFTs are considered to have developed in all the preclinical MTL structures [8]. Although there were differences between the male groups, the pre-AD females demonstrated a steeper rate of decline than non-AD females. Studies have shown that healthy males perform better in SN tasks compared to females [25,26]. Since the years available for analysis in this study are when the NFTs have spread across structures with grid cells and place cells, the male advantage in SN may create a protective factor for episodic memory. The narrative content of the Craft 21 story may be a contributing factor to the pre-AD scoring. If females have a lesser cognitive reserve in this ability than men, then the female episodic memory advantage noted in previous studies may not be a protective factor in the last years of the preclinical stage. However, males were shown to have greater variance in episodic memory scores than females which may contribute to the results for the pre-AD males [28].

One of the strengths of this study is that the pre-AD participants are known to have progressed to AD dementia, so predictive biomarkers were not necessary to differentiate between persons with the disease to those without the disease. The separate analysis of the male and female groups suggests there may be preclinical episodic memory and SN differences among them. This work establishes longitudinal scoring trajectories on Craft 21 paraphrase scoring can be indicator of preclinical AD,

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with significance and effect size, differentiating female participants who will develop AD dementia from those who will not within the NACC UDS.

Implications

The evidence from this study suggests the cognitively unimpaired years of AD demonstrates a distinct difference in episodic memory scores over time compared to those without the disease. Thus, the trajectories of episodic memory change may allow for mapping of AD biomarkers along the established timepoints. In addition to the potential to establish preclinical AD biomarker levels, the findings with the female decline in episodic memory demonstrates the importance of neuropsychiatric test screening for AD in cognitively normal persons to differentiate them from those who do not have the disease. For instance, the past studies demonstrating a female advantage in episodic memory may have had unidentified preclinical persons as participants. Thus, those results may have been influenced by persons with preclinical AD. With an estimated 300 million persons in the preclinical AD stage [1], it may be essential to screen preclinical AD for treatment purposes and defining samples for studies designed to have only cognitively normal participants, such as establishing cognitive normalcy in a domain. This might indicate the need to change the IRB protocol for research on cognitively normal persons screened as positive for AD and ethical considerations regarding how to inform persons as to why they were not selected to be in a sample due to preclinical AD.

The data for this study only reflects the last years of the multi-decade preclinical timeframe, therefore, earlier screening is warranted. Given the youngest age of the pre-AD participants was in the mid-forties, clinical and research screening throughout the adult life span may be more likely to detect the longitudinal biomarker changes in tandem with cognitive change. The male variances in episodic memory should be a consideration for screening.

Limitations

There are limitations to this study. The sample sizes are not equal. The pre-AD male sample size is smaller than the female group. The Craft 21test measures verbal episodic memory but is not a direct measure of SN. Although SN cells are involved with verbal episodic memory, it cannot be assumed there is an equivalent change in external SN activity. Therefore, the test might not serve as a direct proxy for SN and screening for episodic memory along with AD biomarkers may be sufficient to establish the preclinical progression for clinical diagnosis.

Conclusions

Preclinical longitudinal studies to understand potential differences between males and females during the earliest stage may elucidate additional knowledge about episodic memory changes. The development of standardized preclinical cut-off scores for Craft 21 cognitive trajectories may increase specificity in with the standardization of biomarkers. Future studies are needed for evidence of early-stage SN changes in concert with episodic memory change trajectories. Furthermore, the studies should include separate analyses on male and female performance to identify potential differences. This may provide additional validity and data beyond the scope of this study.

Acknowledgments: The NACC database is funded by NIA/NIH Grant U24 AG072122. NACC data are contributed by the NIA-funded ADRCs: P30 AG062429 (PI James Brewer, MD, PhD), P30 AG066468 (PI Oscar Lopez, MD), P30 AG062421 (PI Bradley Hyman, MD, PhD), P30 AG066509 (PI Thomas Grabowski, MD), P30 AG066514 (PI Mary Sano, PhD), P30 AG066530 (PI Helena Chui, MD), P30 AG066507 (PI Marilyn Albert, PhD), P30 AG066444 (PI John Morris, MD), P30 AG066518 (PI Jeffrey Kaye, MD), P30 AG066512 (PI Thomas Wisniewski, MD), P30 AG066462 (PI Scott Small, MD), P30 AG072979 (PI David Wolk, MD), P30 AG072972 (PI Charles DeCarli, MD), P30 AG072976 (PI Andrew Saykin, PsyD), P30 AG072975 (PI David Bennett, MD), P30 AG072978 (PI Neil Kowall, MD), P30 AG072977 (PI Robert Vassar, PhD), P30 AG066519 (PI Frank LaFerla, PhD), P30 AG062677 (PI Ronald Petersen, MD, PhD), P30 AG079280 (PI Eric Reiman, MD), P30 AG062422 (PI Gil Rabinovici, MD), P30 AG066511 (PI Allan Levey, MD, PhD), P30 AG072946 (PI Linda Van Eldik, PhD), P30 AG062715 (PI Sanjay Asthana, MD, FRCP), P30 AG072973 (PI Russell Swerdlow, MD), P30 AG066506 (PI Todd

 doi:10.20944/preprints202406.1984.v1

Golde, MD, PhD), P30 AG066508 (PI Stephen Strittmatter, MD, PhD), P30 AG066515 (PI Victor Henderson, MD, MS), P30 AG072947 (PI Suzanne Craft, PhD), P30 AG072931 (PI Henry Paulson, MD, PhD), P30 AG066546 (PI Sudha Seshadri, MD), P20 AG068024 (PI Erik Roberson, MD, PhD), P20 AG068053 (PI Justin Miller, PhD), P20 AG068077 (PI Gary Rosenberg, MD), P20 AG068082 (PI Angela Jefferson, PhD), P30 AG072958 (PI Heather Whitson, MD), P30 AG072959 (PI James Leverenz, MD).

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