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Association of the digital clock drawing test with amyloid and tau PET biomarkers in low age risk adults

Huitong Ding[1,2], Chenglin Lyu[1], Cody Karjadi[1,2], Preeti Sunderaraman[2,3], Christina B. Young[4], Elizabeth C. Mormino[4], Spencer Low[1], Sherral Devine[1,2], Katherine Gifford[5], Rhoda Au[1,2,3,6,7,8]✉ & Honghuang Lin[9]✉

Although brain amyloid and tau deposition measured by PET scans are established as biomarkers of Alzheimer's disease (AD), they can emerge decades before symptoms are detectable on traditional neuropsychological (NP) tests. There is a pressing need for early AD detection tools that are more accessible, cost-effective, and non-invasive. The digital clock drawing test (dCDT), a digital version of the clock drawing test, has emerged as a promising cognitive assessment tool that takes minutes to administer and can reveal clinical symptoms earlier than paper–pencil NP tests. This study explored the association between 53 dCDT measures and amyloid and tau PET biomarkers using data from 87 low age risk participants in the Framingham Heart Study. Our findings revealed a significant association between a dCDT measure related to spatial reasoning function and global amyloid burden ($P < 0.05$), and 4 dCDT measures correlated with tau accumulation after adjusting for multiple comparisons. Notably, the combination of demographic variables and a composite dCDT score achieved a mean area under the receiver operating characteristics curve of 0.86 in detecting amyloid positivity. These results highlight the potential of dCDT measures as effective predictors of amyloid and tau pathology in preclinical AD.

Keywords Digital clock drawing test, Amyloid, Tau, PET, Association

Alzheimer's disease (AD), a progressive neurodegenerative disorder, poses a significant challenge to global public health, affecting millions worldwide[1]. Its progression is insidious, gradually moving from an undetectable, symptom-free stage to a comprehensive clinical syndrome over the years[2,3]. With limited approved treatments for AD[4], early detection stands out as a critical strategy for managing the disease. While AD biomarkers are necessary for AD disease onset, they are not definitive indicators of future diagnosis[5]. The recent A4 study findings suggest that treatment in the absence of initial clinical symptoms was also not effective[6]. Thus, while the discovery of amyloid and tau proteins as biomarkers for AD has significantly advanced the ability to detect those at AD risk much earlier in its course, its utility is still dependent on evidence of subtle clinical changes, particularly at the preclinical stages[7,8].

Many traditional paper–pencil neuropsychological (NP) assessments have been in use for decades[9–13] and were not initially designed to detect subtle biomarker anomalies present in the initial stages of AD[14]. By the time significant changes are observed in these tests, participants often already have significant pathology, making it too late for the earliest intervention opportunities. The advent of digital cognitive assessment methods, capable

[1]Department of Anatomy and Neurobiology, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA. [2]The Framingham Heart Study, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA. [3]Department of Neurology, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA. [4]Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA, USA. [5]Department of Neurology, Vanderbilt Memory and Alzheimer's Center, Vanderbilt University Medical Center, Nashville, TN, USA. [6]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA. [7]Department of Medicine, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA. [8]Slone Epidemiology Center, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA. [9]Department of Medicine, University of Massachusetts Chan Medical School, Worcester, MA, USA. ✉email: rhodaau@bu.edu; honghuang.lin@umassmed.edu

of capturing a wide array of subtle behaviors opens new avenues as alternative measures to detect initial stages of disease progression in those who are AD biomarker positive.

The digital clock drawing test (dCDT), a digital version of the clock drawing test, has emerged as a promising cognitive assessment tool[15]. The simplicity and non-invasive nature of the dCDT, combined with its ability to be administered quickly by minimally trained examiners makes it a cost-effective attractive alternative for early AD risk screening prior to the use of traditional biomarker assessments. Research has consistently shown its capacity to detect early cognitive deficits in the preclinical and prodromal stages of AD[16,17]. The dCDT has been proven not only to be a valuable tool for assessing risk[16] but also to correlate well with outcomes from established NP tests[17] and MRI assessments of brain volume[18]. A prior investigation explored the relationship between overall and specific scores from the dCDT and the presence of PET amyloid and tau pathology in a population of older adults without cognitive impairments[19]. However, the potential of the diverse array of dCDT measures to mirror the broad range of amyloid and tau PET biomarkers, especially in populations of younger age, has yet to be fully explored.

Investigating the link between subtle behavioral changes detected by dCDT and PET biomarkers in middle-aged and younger (e.g., ≤ 65 years) populations is crucial because the majority of AD cases are late onset (e.g. > age 65). Such research underscores dCDT's value as an early, practical tool for screening AD risk and other neurodegenerative conditions in younger populations, suitable for primary care and broader use. It could position dCDT as a preliminary neurological health assessment that could lead to more targeted, specialized diagnostic evaluations.

The objective of this study is to investigate the association of an extensive collection of dCDT measures and amyloid and tau PET biomarkers across multiple regions within the community-based cohort of middle-aged adults from the Framingham Heart Study (FHS). Furthermore, we fully examined the capability of these dCDT measures in detecting amyloid positivity.

Results

Cohort descriptive

This study included 87 participants (mean age 51 ± 8 years old, 47.1% women) who were deemed cognitively intact. The sample characteristics are shown in Table 1. The description of the dCDT features are presented in Supplemental Table 1. The statistical distribution of each dCDT feature, including minimum, first quartile, median, third quartile, and maximum values, is detailed in Supplementary Table 2. The interrelationships among these features are visually represented through a correlation heatmap in Supplementary Fig. 1. No significant demographic differences were observed between participants who completed both the dCDT and PET imaging, and those who only underwent the dCDT (Supplementary Table 3).

Association between dCDT measures and amyloid and tau PET biomarkers

As shown in Table 2, COPVerticalSpatialPlacement, a measure of the vertical position of the drawing on the page on the copy clock, was associated with the global burden of amyloid with nominal significance ($P < 0.05$). This measure is related to the spatial reasoning function (Supplementary Table 4). We then examined the association of dCDT measures with amyloid positivity. Table 3 shows that six dCDT measures (five pertaining to the simple motor and one to information processing) were significantly associated with amyloid positivity, with odds ratios (ORs) ranging from 0.09 to 3.58 and P values below 0.05. For example, COPPercentInkTime represents the percentage of time actively spent drawing on paper with the pen during the copy clock task. Each standard

Variable	Sample ($n = 87$)
Age (years), mean (SD)	51 (8)
Women, *n* (%)	41 (47.1%)
Education, n (%)	
High school	6 (6.9%)
Some college	27 (31.0%)
College and higher	54 (62.1%)
Mini-Mental State Examination score, mean (SD)*	28.9 (1.1)
Amyloid biomarkers, median (IQR)	
Amyloid positive, *n* (%)	7 (8.0%)
Global burden	0.91 (0.89, 0.94)
Tau biomarkers, median (IQR)	
Entorhinal	1.04 (0.98, 1.10)
Amygdala	1.14 (1.07, 1.20)
Inferior temporal	1.12 (1.07, 1.15)
Inferior parietal	1.03 (0.99, 1.11)
Precuneus	1.06 (1.02, 1.11)
Parahippocampal	1.04 (0.99, 1.10)

Table 1. Sample characteristics. *A total of 16 participants had available Mini-Mental State Examination information.

Biomarker		Significant features, *n*	Most significant dCDT feature		Description	Beta	SE	*P* value
Amyloid	Global burden	1	COPVerticalSpatialPlacement	Copy clock	A measure of the vertical position of the drawing on the page	−0.20	0.10	0.040
Tau	Entorhinal	9	COPLongestLatency	Copy clock	The duration of the longest latency in the drawing	0.36	0.12	0.0044
	Amygdala	4	COPComponentPlacement	Copy clock	A measure of the spatial relationships among the drawing components	0.32	0.12	0.0093
	Inferior temporal	8	COPPercentInkTime	Copy clock	The percentage of the test time spent actively drawing with the pen on the paper	0.31	0.12	0.013
	Inferior parietal	6	COPPercentInkTime	Copy clock	The percentage of the test time spent actively drawing with the pen on the paper	0.36	0.12	0.0042
	Precuneus	9	COPSimpleMotor	Copy clock	The graphomotor components involved in the process	−0.43	0.11	2.9×10^{-4}*
	Parahippocampal	5	COPSimpleMotor	Copy clock	The graphomotor components involved in the process	−0.39	0.11	8.6×10^{-4}*

Table 2. Most significant dCDT features are associated with amyloid (n = 87) and tau PET biomarkers (n = 70). *SE* standard error. *Remained significant after adjusting for multiple comparisons using false discovery rate correction.

dCDT feature		Description	Odds ratio	95% CI	*P* value
Simple motor	COMInitiationSpeed	The speed of the pen when beginning to draw the clock face of the command clock	0.10	0.01–0.41	0.010
	COMAverageSpeed	The average speed of the pen for all pen strokes used during the drawing of the clock face of the command clock	0.21	0.05–0.65	0.016
	COMTerminationSpeed	The speed of the pen when finishing the clock face of the command clock	0.21	0.04–0.65	0.019
	COMMaxSpeed	The maximum speed of the pen on the page during the drawing of the clock face of the command clock	0.29	0.08–0.78	0.025
	COPPercentInkTime	The percentage of the test time spent actively drawing with the pen on the paper for the copy clock	3.58	1.33–12.53	0.022
Information processing	COPPercentThinkTime	The percentage of the test time spent "thinking" (i.e., holding the pen off the page but not actively drawing), measured from the first touch of the pen on the paper to the last pen lift off the paper, on the copy clock	0.28	0.08–0.75	0.022

Table 3. Association between dCDT features and amyloid positivity. *CI* confidence interval.

deviation increase in COPPercentInkTime was associated with 3.58-fold higher odds of amyloid positivity. However, none of these associations were significant after adjusting for multiple comparisons.

Among the 87 participants with amyloid data, tau measurements were collected from 70 participants. Forty-eight dCDT measures showed significant associations, as every one of the seven tau biomarkers was associated with at least four dCDT measures (Table 2). Notably, seven dCDT measures related to information processing function have associations with tau biomarkers. After adjusting for multiple comparisons using false discovery rate correction, four dCDT measures remained statistically significant. Notably, three of these were associated with tau accumulation in the precuneus region. The most significant association was between COPSimpleMotor, which assesses basic motor skills during the drawing task, and tau accumulation in the precuneus region (beta = -0.43, SE = 0.11, $P = 2.9\times10^{-4}$).

Four dCDT measures related to simple motor and information processing were found to be associated with both amyloid positivity and tau biomarkers (Table 3, Supplementary Table 4). All association results can be found in Supplementary Tables 5–7.

Performance of dCDT measures for detecting amyloid positivity

We further assessed the discrimination capability of dCDT measures for amyloid positivity. Figure 1 displays the ROC curves for two models. Model 1, including only clinical risk factors (age, sex, and education), reached an AUC of 0.66. Model 2, additionally including the composite dCDT score, reached superior performance with an AUC of 0.86.

Discussion

Amyloid and tau deposition measured by PET scans are recognized as biomarkers of AD, yet their high cost limits widespread use. Therefore, this study explored the effectiveness of dCDT as a practical, cost-effective method for the early detection of AD by examining the association of dCDT measures with amyloid and tau PET biomarkers in adults who are largely below the age risk for late-onset AD, which is the common type of AD. The investigation into this association not only has the potential to validate the dCDT as a reliable early screening tool but also to advance our understanding of cognitive markers that correlate with molecular changes in the brain.

The association of dCDT measures with amyloid and tau pathology, particularly the significant association between the parahippocampal tau region and the COPSimpleMotor feature, highlights the relevance of graphomotor functions in the context of neurodegenerative disease[20]. This finding suggests that the mechanics of drawing, encapsulated by the COPSimpleMotor, may serve as a sensitive indicator of tau accumulation in specific

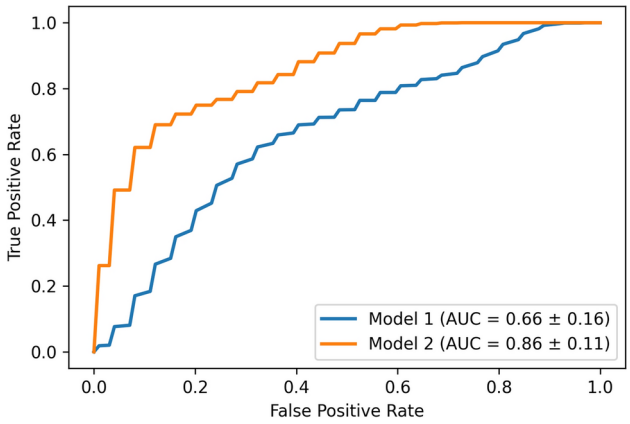

Fig. 1. ROC curves of three models to identify amyloid positivity. Model 1 incorporates age, sex, and education; Model 2 extends upon Model 1 by including a composite dCDT score, which was derived from dCDT measures that have shown significant association with amyloid positivity.

brain regions. Furthermore, the discovery that dCDT measures for three cognitive functions including simple motor, spatial reasoning, and information processing correlate with both amyloid and tau biomarkers reinforcing the multifaceted nature of cognitive function and the complex interplay between different cognitive domains and pathological processes. Drawing efficiency typically evaluates how quickly and effectively a participant completes the drawing task, which can reflect underlying cognitive and motor processes[21]. Our study indicated that drawing efficiency was significantly associated with tau biomarkers but not with amyloid biomarkers. This distinction is important as it suggests that tau pathology, which is closely linked to neurodegenerative processes affecting cognitive domains like memory and spatial awareness[22,23], may directly influence motor skills and drawing performance. These findings are crucial as they help refine our understanding of how different biomarkers relate to specific cognitive functions, especially when AD clinical symptoms are below the threshold for clinical diagnosis. This study also identified associations between dCDT measures and the putamen, a control region used to access off-target binding. However, these associations did not remain significant after multiple comparison corrections. Previous research has noted increased uptake patterns in the putamen, particularly in individuals with movement disorders such as corticobasal degeneration[24]. Further research is needed to better understand these associations, which could help establish dCDT as a valuable tool for biomarker-specific cognitive assessments. We found certain features capturing subtle participant behaviors during the test process were related to amyloid and tau pathology. This observation underscores the superior capability of digital features captured by digital pens in detecting amyloid and tau pathology, potentially identifying these conditions earlier than what the overall scores from cognitive tests can achieve. dCDT captures fine-grained, process-based aspects of cognitive and motor function, which may vary by brain region. For example, COPPercentThinkTime reflects the time spent thinking before initiating drawing, showed opposite associations with tau in the inferior temporal and inferior parietal regions, suggesting region-specific effects on cognitive processing. These relationships may not be linear, as some dCDT metrics could indicate compensatory mechanisms in early pathology, while others reflect direct impairment at later stages. Future longitudinal studies are needed to further clarify these associations. Furthermore, most significant associations with amyloid and tau PET biomarkers were observed in dCDT measures from the copy task, with some measures from both tasks showing similar tau accumulation patterns. For example, the percentage of the test time spent actively drawing and the percentage of the test time spent thinking were associated with tau burden in inferior temporal and inferior parietal regions in both tasks. This distinction likely reflects the different cognitive demands of each task. The command task relies on executive control, whereas the copy task primarily assesses visuoconstructional ability[25].

Particularly for younger participants, this study underscores the robustness of dCDT measures as predictors of amyloid positivity, offering promise for their application in younger populations at risk of AD. The association of COPPercentInkTime with amyloid positivity further emphasizes the importance of incorporating measures of drawing engagement in the assessment of neurodegenerative disease risk[26]. Prior research has investigated the correlation between the overall scores and sub-domain composite scores of the dCDT and PET amyloid and tau pathology among the elderly population[19], but did not have more item-specific measures to consider. This study advances our understanding by identifying finer dCDT features related to these biomarkers among a younger aged population, indicating that the dCDT can detect even more subtle pathology changes when disease modifying interventions may be more effective. These findings suggest that before any significant correlations manifest in the overall scores, dCDT might already highlight abnormalities in the amyloid and tau pathology. Thus, our research would be a valuable complement to earlier studies on life course correlations, demonstrating the potential of dCDT for the early detection of neurodegenerative disorders.

While individual dCDT measures may vary in effect size, their combined predictive value enhances the detection of amyloid positivity. The integration of multiple dCDT measures together with age, sex, and education reached an AUC of 0.86, suggesting a potential new approach in the screening and monitoring of AD. Furthermore, dCDT is non-invasive, cost-effective, and scalable, making it a promising tool for large-

scale population screening, especially in settings where traditional neuroimaging is not feasible. These findings support the integration of dCDT measures into early assessment protocols to improve early detection strategies.

The main strength of this study lies in its inclusion of adults below the age of late-onset AD with a wide array of digital metrics that capture subtle behavioral variations, along with the utilization of amyloid and tau PET data across various brain regions. This approach offers a comprehensive characterization of associations, enhancing our understanding of the intricate relationships between digital test metrics and neurodegenerative pathology in middle life. We acknowledged the exploratory nature of this study. The relatively small sample size and the demographic homogeneity, with participants predominantly of White European descent, may restrict the generalizability of the findings. Although our results indicate that there are no significant demographic differences between our sample and the larger sample with the dCDT, more participants are needed to enhance the representativeness of our sample. These factors underscore the necessity for future research to be conducted on a broader scale, incorporating larger and more diverse populations. Moreover, some dCDT features may be more closely linked to biofluid markers in the earliest stages of AD. Future research integrating both PET and biofluid markers will be crucial in determining whether digital cognitive markers align more strongly with biofluid or imaging-based biomarkers across different stages of the disease. Besides, including other neurodegenerative biomarkers in future studies could help clarify whether dCDT and tau associations are specific to AD or reflective of broader tau-related neurodegeneration. Our sample consists of relatively young participants, many of whom are amyloid-negative, reducing the likelihood of tau positivity. Future research could explore the predictive ability of dCDT for tau positivity.

In conclusion, the demonstrated efficacy of dCDT measures in predicting amyloid positivity in middle-aged adults invites further exploration into their application in AD assessment. Future studies should aim to validate these findings in larger and more diverse cohorts, explore longitudinal relationships, and investigate the utility of combining dCDT measures with other biomarkers to refine predictive models for cognitive impairment.

Methods

Study participants

FHS, initiated in 1948, is a longitudinal cohort study rooted in a community setting, engaging three successive generations of participants to date. Detailed descriptions of the FHS cohorts, encompassing its organizational framework and the demographic profiles of its participants, have been thoroughly outlined in previous studies[27–29]. The participants from the Offspring and Third Generation cohorts who underwent both the dCDT assessment and PET imaging in their middle to young-old age (≤65 years old[30–32]), which is below the age of risk for late-onset AD[33], were included in this study (Supplemental Fig. 2). None of the participants had a diagnosis of dementia or mild cognitive impairment at the time of the PET scan. More information on dementia surveillance of FHS can be found in previous studies[34–36]. This study's methodologies and protocols received approval from the Institutional Review Board at Boston University Medical Campus. All participants provided their written informed consent before participating. All methods were carried out in accordance with relevant guidelines and regulations.

Brain PET imaging

PET scans of FHS participants were conducted using either a Siemens ECAT HR+ camera or a GE Discovery MI camera, with 11C-Pittsburgh Compound B for amyloid and 18F-Flortaucipir for tau imaging[37–42]. Cerebellum cortex was used as the reference region. The details for the amyloid and tau PET acquisition and processing have been previously reported[43]. In summary, for amyloid PET imaging, a global composite score for each participant was derived by computing the volume-weighted average of the frontal, anterior cingulate cortex/posterior cingulate cortex, lateral parietal, and lateral temporal regions[44]. Gaussian mixture modeling was utilized on the global composite scores, revealing two distinct distributions. A distribution volume ratio threshold that corresponded to a 90% likelihood of association with the amyloid-beta positive cluster was established to assess amyloid positivity. In tau PET analysis, volume-weighted standardized uptake value ratios were computed for six regions of interest, including bilateral entorhinal, amygdala, inferior temporal, inferior parietal, precuneus, and parahippocampal areas[45].

Digital clock drawing test (dCDT)

Beginning in October 2011, participants of FHS have supplemented their routine neuropsychological evaluations with the dCDT[15,46–48]. This innovative approach employs a digital pen provided by Anoto Inc., enabling participants to draw a clock on specially designed paper marked with a discrete dot pattern. This digital pen is equipped with a camera that captures the pen's movements at a high frequency (80 times per second) and with fine precision (a spatial resolution of 0.002 inches)[46,47]. This technology is designed to facilitate the categorization of various elements of the drawing, such as numerals, clock hands, and other lines. Adhering to the established protocols of the traditional clock drawing test, the dCDT incorporates both "command" and "copy" test conditions. The details of the administration process are described in a previous study[49].

This study incorporates 53 distinct features from the dCDT that track the drawing process, encompassing every stroke made and their respective timing delays. These features collectively assess various cognitive abilities, including drawing efficiency, simple motor skills, speed of processing information, and the capacity for spatial reasoning (Supplemental Table 1). More descriptions of these features can be found in previous studies[50,51]. All dCDT features underwent a rank-based inverse normal transformation to mitigate skewness in their distribution.

Statistical analyses

This study examined the association between dCDT features and global burden for amyloid PET, as well as tau PET in seven regions using linear regression models, adjusting for age, sex, education, and the time interval

between dCDT examination and PET scans. Additionally, in the tau PET analysis, adjustments were made to further account for amyloid positivity.

The association of normalized dCDT features with amyloid positivity was assessed by logistic regression models, adjusting for age, sex, education, and the time interval between dCDT examination and PET scans. Based on the regression coefficients, the ORs and 95% CIs were estimated. In each model, continuous variables for both exposure and outcomes were standardized as z scores to ensure consistency in the analysis. False discovery rate correction was used to adjust for multiple tests. A composite dCDT score was formulated as a weighted combination of dCDT features that were significantly associated with amyloid positivity, using the coefficients from the logistic regression model.

To evaluate the performance of dCDT measures for identifying amyloid positivity, a logistic regression model was built based on age, sex, educational level, and the composite dCDT score. Considering the relatively small sample size, to evaluate model performance robustly, the data were split into training and testing sets 1000 times, with each split comprising 60% training and 40% testing data, ensuring stratification of the target variable (amyloid positivity) to maintain class proportions. To address potential class imbalance, the synthetic minority over-sampling technique was applied to the training data[52]. Post-resampling, all continuous predictor variables were standardized to ensure that model inputs were on a comparable scale. For comparison, a base model was built based on age, sex, and educational level. Receiver operating characteristic (ROC) curves were plotted to visually compare the performance of the two models.

Data availability

The datasets analyzed for this study could be requested through a formal research application to the Framingham Heart Study[53].

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Author contributions

H.D. drafted the manuscript. H.D. and C.L. performed the main analysis. R.A. and H.L. supervised the study. All authors participated in the interpretation of the results. All authors reviewed the manuscript.

Declarations

Competing interests

RA is a scientific advisor to Signant Health and NovoNordisk. The other authors state that this study was carried out without any commercial or financial affiliations that might be seen as a possible conflict of interest.

Additional information

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Correspondence and requests for materials should be addressed to R.A. or H.L.