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Evaluating Digital Cognitive Biomarkers as a Noninvasive Diagnostic Tool for Alzheimer's Disease: Correlations with Classic CSF Biomarkers

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EVALUATING DIGITAL COGNITIVE BIOMARKERS AS A NONINVASIVE DIAGNOSTIC TOOL FOR ALZHIEMER'S DISEASE: CORRELATIONS WITH CLASSIC CSF BIOMARKERS

by

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ABSTRACT

Alzheimer's Disease (AD) is a neurodegenerative disorder affecting over 35 million people. Early diagnosis and intervention are crucial for improving outcomes. Digital Cognitive Biomarkers (DCBs) offer a promising approach for early detection and disease management, quantifying cognitive processes of encoding and retrieval through a hierarchical Bayesian cognitive processing model using wordlist memory tests. We hypothesize that DCBs will correlate with classic AD cerebrospinal fluid (CSF) biomarkers (Aβ42, T-tau, p-tau) in patients with varying cognitive decline levels compared to healthy elderly controls. Using Alzheimer's Disease Neuroimaging Initiative (ADNI) data and paired Pearson correlation coefficient analysis, our results support the hypothesis, indicating that DCBs correlate with CSF biomarkers and demonstrating their potential as a noninvasive diagnostic tool for AD. Furthermore, DCBs exhibited improved diagnostic accuracy compared to classic AD CSF biomarkers, as indicated by the area under the Receiver Operating Characteristic curve analysis. DCBs hold promise for monitoring disease progression, response to therapeutics, and identifying patients at earlier disease stages. Future research should validate these findings in diverse populations and conduct longitudinal studies to assess DCBs' potential in tracking disease progression and treatment response. Integrating DCBs with other diagnostic approaches, such as neuroimaging, could enhance overall AD diagnosis accuracy and provide a comprehensive understanding of an individual's cognitive health. In conclusion, DCBs may offer a valuable, noninvasive tool for early diagnosis and management of Alzheimer's Disease, supporting the initial hypothesis.

DEDICATION

Dedicated to my father, whose battle with Alzheimer's disease touched the lives of all who knew him. Your strength, kindness, and struggle continue to motivate me every day. Your memory will live on through the love and memories you shared with us, and I will always be grateful for the time we had together. Rest in peace, Dad.

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INTRODUCTION

Alzheimer's disease (AD) is a progressive and neurodegenerative disorder that results in cognitive decline, memory loss, and impaired functioning of daily activities. It is the most common form of dementia and is responsible for up to 70% of cases. It affects more than 35 million people globally, and the incidence of the disease is expected to double every 20 years owing to population aging (Prince, 2013). Despite advances in AD research, there is still no cure for this disease. The current treatments available are symptomatic and only provide a modest improvement in symptoms for a limited time. Therefore, the development of new diagnostic tools and therapies is of utmost importance to provide better care to individuals with AD and their families.

AD is characterized by the presence of amyloid-β (Aβ) protein plaques and hyperphosphorylation of tau protein, which lead to neuronal dysfunction and death. The disease has a long preclinical phase, which can last for many years before the onset of clinical symptoms. During this preclinical phase, there is an accumulation of Aβ plaques and tau tangles in the brain, which are thought to be the main pathological hallmarks of AD. The clinical symptoms of AD are thought to result from the neuronal damage and death caused by these pathological changes (Long, 2019).

The current diagnostic guidelines for AD are described in three stages: preclinical, mild cognitive impairment (MCI), and Alzheimer's dementia. The preclinical stage is characterized by the presence of Aβ and tau biomarkers in cerebrospinal fluid (CSF) and brain imaging studies. However, it is still not possible to predict which cognitively healthy people will and will not advance to MCI or dementia (Sperling et al., 2011). The development of new biomarkers that

can accurately predict the transition from preclinical to clinical stages of the disease is critical for early diagnosis and intervention. Biomarkers are measurable indicators of biological processes that can provide valuable information about disease pathology and progression. CSF biomarkers for AD measure β-amyloid 42, which produces amyloid plaques in the brain, tau, and phospho-tau, which produce tau tangles in the brain, another characteristic of Alzheimer's (Lewczuk & Kornhuber, 2011). These CSF biochemical indicators (biomarkers for AD) may accurately predict the transition from MCI to Alzheimer's dementia with a rate of over 80% (Hampel et al., 2008). The improvement of early and noninvasive AD diagnosis is needed. It is of interest to investigate new noninvasive biomarkers that may be useful to add significant diagnostic value for the realistic monitoring of patients. The focus of AD research has changed from moderate AD stages to asymptomatic or preclinical phases, when the cognitive changes may be very subtle and challenging to assess (Rafii & Aisen, 2019). Therefore, the development of more sensitive biomarkers that can detect cognitive changes in the preclinical phase is crucial for the early diagnosis and treatment of AD.

One promising approach to developing new biomarkers is to use Digital Cognitive Biomarkers (DCBs). DCBs are generated with a hierarchical Bayesian cognitive processing (HBCP) model that utilizes data from common World List Memory (WLM) tests (Bock et al., 2021). WLM tests are commonly employed to detect cognitive impairment or dementia phases of Alzheimer's disease (AD) in patients before neuroimaging or other examinations, as well as to track treatment responses (Salmon & Bondi, 2009). Since the focus of AD research has changed to asymptomatic or preclinical phases, this has encouraged the research community to review the WLM tests that they employ and construct more complex scoring to attain the highest level of measurement precision (Aisen et al., 2017). Newly developed Digital Cognitive Biomarkers

(DCBs) quantify cognitive processes of encoding and retrieval and serve as biomarkers for diagnostics and monitoring disease progression (Bock et al., 2021). By verifying whether cognitive performance measured by DCBs correlates with CSF biomarkers levels, we can understand the potential usefulness of DCBs in early diagnosis and disease management.

Using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) data inventory, associations between DCBs and classic AD CSF biomarkers will be investigated using paired Pearson correlation coefficient analysis. We hypothesized that Digital Cognitive Biomarkers will be correlated with the AD classic CSF biomarkers Aβ42, T-tau, and p-tau in patients with varying levels of cognitive decline, as compared to cognitively healthy elderly population control participants. In addition, we assessed the diagnostic accuracy of each DCB domain separately and the combined DCB score for Alzheimer's disease using Receiver Operating Characteristic (ROC) curve analysis. The ROC curve was compared to a CSF biomarker ROC. We predicted our results will show that the DBCs correlate with CSF biomarkers, supporting that DCBs could provide valuable insight and eventually become increasingly useful in monitoring disease progression and response to therapeutics. In addition, DCBs could contribute to more accessible diagnostics available at varying levels of care throughout disease progression. With an aging population, we will require advances in the evaluation of the underlying cognitive process in individuals with dementia and Alzheimer's Disease. DCBs could prove a powerful tool in the characterization of underlying cognitive processes and how they are affected by aging, disease progression, and therapeutic interventions.

BACKGROUND

Alzheimer's disease (AD) is the most prevalent neurodegenerative cause of dementia, accounting for 60% to 80% of dementia cases ("2022 Alzheimer's disease facts and figures", 2022). It affects more than 35 million individuals globally, with 6.5 million of those individuals in the United States ("2022 Alzheimer's disease facts and figures," 2022). Its incidence is predicted to double every 20 years owing to population aging (Prince et al., 2013). AD is characterized by alterations including the buildup of Aβ plaques and protein tau tangles in the brain (Rajmohan & Reddy, 2017). Neuronal loss and brain tissue damage accompany these alterations (Jack et al., 2018).

Symptoms

The current diagnostic guidelines of AD are described in 3 stages: preclinical, mild cognitive impairment (MCI), and Alzheimer's dementia (Croisile et al., 2012) The preclinical stage includes amyloid aggregation and other brain changes that do not yet exhibit visible clinical symptoms (Mayo Clinic, 2018). The MCI stage includes abnormal cognitive problems that do not interfere with independence (Mayo Clinic, 2018). Alzheimer's dementia includes the final stage in which memory and spatial problems are substantial enough to limit one's capacity for independent functioning (Croisile et al., 2012). The damaged areas of the brain include the hippocampus, frontal lobe, and temporal lobe, which are the memory, thought-related, and language areas of the brain, respectively (Mayo Clinic, 2018). Degeneration of cholinergic neurons, particularly in the basal forebrain, is also a significant contributing factor in Alzheimer's disease, leading to a decline in acetylcholine levels and impairing cognitive functions (Mayo

Clinic, 2018). As a result, memory, language, and thinking issues are frequently among the early signs of Alzheimer's disease (Mayo Clinic, 2018). The brain changes that lead to these symptoms are believed to start 20 years or more before symptoms appear ("2022 Alzheimer's disease facts and figures," 2022). The most well-known symptoms of AD include memory loss, decreased communication, disorientation, confusion, poor judgment, and behavioral abnormalities (Atri, 2019). In addition, apathy and depression are common early symptoms, as is forgetting recent conversations, names, or events. Later signs and symptoms include difficulties in several motor functions that involve speaking, walking, and swallowing (Atri, 2019; Braak et al., 2011).

Diagnosis

Previously, AD could only be definitively diagnosed at death. An autopsy could reveal distinctive plaques and tangles (NIA, 2020). Now, AD can be identified during life with greater accuracy. Biomarkers can identify the plaques and tangles through specialized PET scans or by identifying amyloid and tau proteins in plasma and CSF (Wolk DA, 2020). A diagnostic workup would most likely include neurological and neuropsychological testing, a variety of brain imaging, and CSF biomarkers (Albert et al., 2011). Memory is tested, as well as other mental processes, during neuropsychological testing (Albert et al., 2011). Brain imaging can be used to rule out diseases other than AD that could cause similar symptoms, such as tumors or strokes. Typical imaging includes MRI to look for brain shrinkage in areas of the brain linked to AD and CT scans to rule out head traumas, strokes, and malignancies (Albert et al., 2011). Doctors may be able to identify certain brain alterations with specialized imaging, which is mostly utilized in large hospitals or clinical studies (NIA, 2022). These techniques use PET scans to evaluate the amount of neurofibrillary tangles and amyloid deposits in the brain. Finally, the abnormal beta-

amyloid and tau levels in the CSF fluid may be measured using further testing (NIA, 2022).

An international diagnostic criterion for AD was proposed by the National Institute of Aging-Alzheimer Association (Albert et al., 2011). Diagnosis is based on biomarkers found in cerebrospinal fluid (CSF), MRI, and PET, including amyloidosis, tau pathology, and neurodegeneration (Sperling et al., 2011). The "AD signature" in CSF, which is defined as a reduced concentration of Aβ42 with an increase in total tau protein (t-Tau) and hyperphosphorylated tau (p-Tau), is one of the most well-established molecular indicators for dementia (Albert et al., 2011). International standards include this CSF profile as a supportive diagnostic criterion (Albert et al., 2011).

Treatment

Although there is no known cure for Alzheimer's, there are medications that might slow the disease's course and alleviate some of its symptoms. Cholinesterase inhibitors and memantine are two types of medication now utilized to treat AD (Parsons et al., 2013). Acetylcholine, a neurotransmitter that Alzheimer's disease depletes in the brain, is preserved by cholinesterase inhibitors (Sharma, 2019). Memantine inhibits the release of the neurotransmitter glutamate, which stops an excessive amount of calcium from entering the brain cells and fights neuronal death from excitotoxicity (Robinson & Keating, 2006). The Food and Drug Administration (FDA) authorized aducanumab (Aduhelm) for the treatment of certain Alzheimer's patients in June 2021. This is the first medication authorized for use to remove amyloid plaques in the brain, which are a hallmark of Alzheimer's disease (Beshir et al., 2022). Unfortunately, Alzheimer's disease is neither reversed nor cured with aducanumab. After 18 months, it decreased the levels of amyloid plaque in 2 clinical studies, however, neither one saw any clinical effects (Woloshin

& Kesselheim, 2022). In addition, side effects, such as brain swelling, were common in patients. The FDA has mandated that a new study be finished by 2030 to determine whether aducanumab offers a meaningful benefit (Woloshin & Kesselheim, 2022).

CSF AD Biomarkers

CSF biomarkers are a promising diagnostic tool for AD diagnosis. In the pre-clinical stage, NORMALassociated biomarkers already exhibit aberrant concentrations, enabling early AD diagnosis even before the emergence of symptoms (De Meyer et al., 2010). Due to the direct interaction between the brain's interstitial fluid and the CSF, CSF biomarkers are favored over blood/plasma biochemical indicators in AD to represent brain pathology. Through the blood-brain barrier's constrained movement of chemicals and proteins, the CSF is protected from the peripheral system's direct effect (Olsson et al., 2016). As a result, CSF analysis is useful for identifying neurodegenerative disease biomarkers *in vivo*. The three primary pathological alterations that take place in the AD brain— amyloid (Aβ) deposition into extracellular Aβ plaques, the development of intracellular neurofibrillary tangles (NFTs), and neuronal loss—are individually linked with CSF biomarkers (Jansen et al., 2015). The transmembrane amyloid precursor protein (APP), which has 42 amino acids ($A\beta_{1-42}$), is broken down by secretases, including α-secretase, β-secretase (BACE1), and γ-secretase, to produce the amyloid peptide (Jansen et al., 2015). A lower CSF $A\beta_{1-42}$ content in AD is indicative of the extracellular Aβ deposits that form in the brain due to Aβ's insoluble nature (Niemantsverdriet et al., 2017). Tau proteins are widely distributed in the cytoplasm of neurons, where they serve to keep microtubules in place (Jansen et al., 2015). Tau is hyperphosphorylated in AD due to an imbalance between kinases and phosphatases, which causes tau to detach from microtubules and

accumulate into NFT (Jansen et al., 2015). Tau and phosphorylated tau proteins are released into the extracellular environment throughout disease progression, leading to higher CSF tau concentrations in AD (Jansen et al., 2015). The development of plaques and NFT increases neuronal damage and, as a result, synaptic and neuronal degeneration (Jansen et al., 2015). The first Aβ plaques appear at least ten years before the first symptoms, most likely twenty to thirty years before the first symptoms, and are therefore detectable in the CSF for early diagnosis (Jansen et al., 2015). In contrast to CSF Aβ1-42, CSF tau biomarkers manifest later in the pathophysiological process, and CSF tau is more strongly linked with cognitive deterioration than $A\beta_{1-42}$), (Buchhave et al., 2012; Savva et al., 2009). CSF biomarkers may provide accurate and early detection of AD pathophysiology, though an invasive lumbar puncture is required.

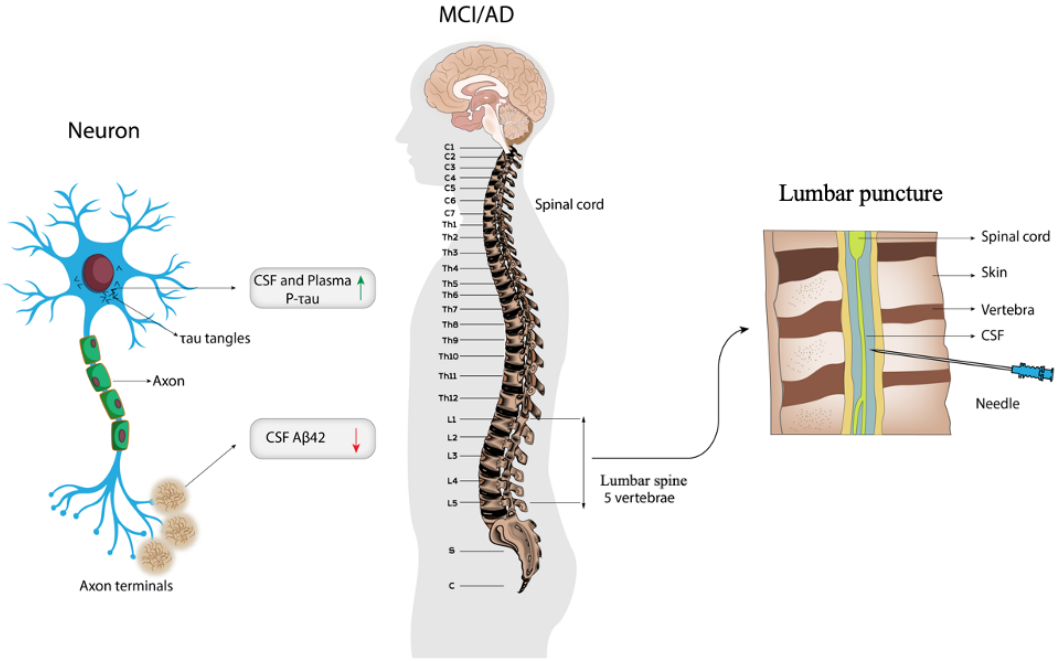

Figure 1: Accumulation of p-tau and Aβ42 in a neuron and subsequent collection of CSF through lumbar puncture for diagnostic testing

Although CSF biomarkers correlate with pathophysiology, there remains a discrepancy in the correlation with cognitive function. According to reports, the presence of some standard biomarkers is correlated with cognitive function (Bertens et al., 2015; Rolstad et al., 2011). However, this connection is still debatable (Williams et al., 2011). Reports from earlier investigations on the relationship between cognitive function and biomarkers have varied (Ibarra et al., 2021). While numerous previous research has identified an association between episodic memory and biometric marker concentrations (Ibarra et al., 2021; Reijs et al., 2017), one study showed no correlation in several elements of cognition (Ibarra et al., 2021).

The majority of cross-sectional investigations at various clinical phases (Vemuri et al., 2009) were unable to establish a relationship between global cognition and CSF biomarkers (Spies et al., 2010). However, in one study, amyloid positive deposition was associated with worse cognitive performance than amyloid-negative deposition in older adults who were cognitively sound (Duke Han et al., 2017). Longitudinal investigations on an older population in good cognitive health have shown that participants who were amyloid positive had a more pronounced cognitive deterioration over time than those who were amyloid negative (Stomrud et al., 2010). A contrasting study did not find a correlation between biomarker levels and cognitive decline in patients with mild dementia and AD (Vemuri et al., 2010). The Mini-Mental State Examination (MMSE) and memory tests in AD populations were found to be negatively correlated with CSF total-tau levels in another investigation (Dumurgier et al., 2017). Another aim of this study is to further examine whether CSF biomarkers might be used to indicate AD cognitive deterioration utilizing the latest cognitive tests in digital cognitive biomarkers (DCB), given the differences between prior findings.

Digital Cognitive Biomarkers

The significant socioeconomic and medical costs associated with Alzheimer's disease (AD) have radically changed the focus of some clinical research toward early detection and intervention (Cummings et al., 2018). This change has been in line with FDA advice supporting earlier-stage medicines and improved measuring techniques for demonstrating such therapies' clinically significant benefits (Bock et al., 2021).

For certain cognitive domains, current common neuropsychological testing cannot be used. The Mini-Mental State Examination (MMSE(is a frequently used neuropsychological test in AD research (Vemuri et al., 2010). The Cambridge Cognitive Test (CAMCOG), the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery are three shorter but more thorough tests than the MMSE (Rami et al., 2011). Another aim of this study is to examine the application of DCBs in the setting of health care, where neuropsychological examination of underlying cognitive processes is not feasible with current testing.

Hence, Embic Corporation’s digital cognitive biomarkers (DCBs) will be used for this study, which quantify underlying cognitive processes of encoding and retrieval that have been previously inaccessible (Bock et al., 2021). Embic’s DCBs facilitate a non-invasive and pragmatic approach to characterizing cognitive function at a granular level, which enables the identification and quantification of subtle but meaningful cognitive changes (Bock et al., 2021). The DBCs are obtained through the combination of Embic’s normative database of cognitively healthy adults, with a hierarchical Bayesian cognitive processing (HBCP) model, applied to item response data from commonly used wordlist learning, recall, and recognition tasks (Lee et al., 2020). HBCP-generated DCBs revealed the capacity to identify individuals with impending

cognitive impairment from those who stay cognitively normal, utilizing baseline, item-response data from a WLM test (Bock, 2019). This study aimed to demonstrate the ability of HBCP models to predict amyloid presence with noninvasive cognitive testing (J. R. Bock et al., 2019).

Digital cognitive biomarkers can identify more subtle cognitive changes in a patient (Bock et al., 2020). This may provide a new avenue for monitoring biomarker disease progression of biomarker through focusing specifically on differences in memory and retrieval (Bock et al., 2021). This study aims to further develop the use of DCBs to predict cognitive decline in patients and monitor stage progression through the accumulation of biomarkers. Successful investigations could validate the use of DCBs in the characterization of underlying cognitive processes and how they are affected by aging, disease progression, and therapeutic interventions.

The development of more sensitive cognitive evaluation measures, such as composite scoring, has been the focus of several initiatives, such as PACC and ADCOMS (Donohue et al., 2014; Wang et al., 2016). Even while these diagnostic measures can perform better than less sensitive tests created to gauge the degree of dementia, as a whole PACC and ADCOMS are unable to foresee imminent cognitive deterioration in individuals cognitively normal. (Bock et al., 2021). Recently, Hierarchical Bayesian cognitive process (HBCP) models applied to data from a wordlist memory (WLM) test have led to the development of one such evaluation strategy (J. Bock et al., 2019). With this method, digital cognitive biomarkers (DCBs) may be produced that are related to the implicit cognitive processes of encoding, storing, and retrieval from different learning and memory states (J. Bock et al., 2019). Such cognitive processes are difficult to examine or quantify directly, but DCBs may quantify these processes and offer information about cognitive function that conventional evaluation methods do not (Lee et al., 2020).

However, due to the complex character of AD pathogenesis and its heterogeneous clinical presentation, it is doubtful that a single biomarker can attain the greatest possible predictive accuracy in patients with cognitive symptoms on its own. Therefore, it is now necessary to determine which additional measurements biomarkers should be combined with to produce an accurate prediction of future AD and to create the best diagnostic algorithm of non-invasive, economically viable, and readily accessible techniques for early diagnosis of AD (Palmqvist et al., 2021). Digital cognitive biomarkers may prove to be another easily available, noninvasive tool that may be utilized in conjunction with other noninvasive biomarkers, such as plasma phosphorylated tau, to track disease development and biomarkers early on in clinical evaluation.

METHODS

Participant Data

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael NORMAL. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). There were 2,258 subjects in this database, with 10,398 assessments Data access was granted in November 2022.

CSF Biomarkers

Data was acquired for CSF Aβ42, t-tau, and p-tau from the ADNI website (normal.loni.ucla.edu/ADNI). The ADNI procedural manual, which can be accessed at normal.adni-info.org, provides guidance on CSF collection and transport procedures, as well as procedural specifics for assessing CSF Aβ42, t-tau, and p-tau181. A summary for these procedures follows.

The CSF was collected in the morning, following an overnight fast, using a 20- or 24-gauge spinal needle. Within one hour of collection, the CSF was frozen and transported on dry ice to the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center. The measurements for Aβ42, t-tau, and p-tau181 were conducted using the Innogenetics (INNO-BIA AlzBio3; Ghent, Belgium) immunoassay kit-based research-use only reagents, containing

4D7A3 monoclonal antibody for Aβ42, AT120 monoclonal antibody for t-tau, and AT270 monoclonal antibody for p-tau181. The multiplex xMAP Luminex platform (Luminex Corporation, Austin, TX) was used for the measurements. All CSF biomarker assays were performed in duplicate and then averaged (Shaw et al. 2009).

Generating Digital Cognitive Biomarkers

Embic's ten digital biomarkers, each of which assesses a certain cognitive encoding or retrieval process, are included in the ADNI dataset. DCBs were calculated for each ADAS-Cog WML assessment and were included for 2,258 subjects (10,398 assessments), dates ranging from 5/17/2005 to 11/1/2021.

Biomarker Label	Biomarker Name	Biomarker Description
N1	One-shot Learning	Probability of encoding into the DURABLY LEARNED State
N2	Transient Learning	Probability of encoding into the TRANSIENTLY LEARNED State
N3	Consolidated Learning	Probability of encoding into the DURABLY LEARNED State, following previous TRANSIENT LEARNING (N2)
N4	Testing Effect Learning	Probability of encoding into the DURABLY LEARNED State, due to successful retrieval (R1) from the TRANSIENTLY LEARNED State
R1	Transient Retrieval	Probability of retrieving from the TRANSIENTLY LEARNED State
R2	Immediate Durable Retrieval	Probability of retrieving from the DURABLY LEARNED State
R3	Delayed Durable Retrieval	Probability of retrieving from the DURABLY LEARNED State after a 5-minute delay with distraction
M1	Recall	Probability of immediate recall of a non-durably stored episodic memory
M2	Recall	Probability of immediate recall of a durably stored episodic memory
M3	Recall	Probability of delayed recall of a durably stored episodic memory

Table 1. Available Digital Cognitive Biomarkers for ADNI ADAS-Cog WML tests.

Statistical Analysis

To analyze the associations between digital cognitive biomarkers (DCBs) and classic Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarkers (AB, t-tau, and p-tau), paired Pearson correlation coefficient analyses were performed with t-tau, p-tau, and AB as dependent variables in separate models. There were 2,258 subjects in this database, with 10,398 assessments. All scores were averaged over multiple visits resulting in N=775, among which 553 patients were diagnosed AD+ and 222 were normal. The combined DCB score is defined as N1+N2+N3+R1+R2+R3+M1+M2+M3. (N=775, among which 553 patients were diagnosed AD+ and 222 were normal. Statistical significance was set at $p < 0.001$. Additionally, separate paired Pearson correlation coefficient analyses were conducted for each diagnostic group (cognitively normal, mild cognitive impairment (MCI), and AD) to investigate the relationship between DCB Total and the CSF biomarkers. The strength of the associations between the predictor variables and the dependent variables was quantified using Pearson correlation coefficient (r). Effect sizes were calculated using Cohen's d to compare the differences between the AD+ and normal groups in each domain of DCB. Receiver Operating Characteristic (ROC) curve analyses were performed to assess the diagnostic accuracy of each DCB domain and the combined DCB score for Alzheimer's disease. Area Under the Curve (AUC) values were calculated as a single measure of diagnostic accuracy. The diagnostic accuracy of cerebrospinal fluid (CSF) biomarkers, namely tau, phosphorylated tau (p-tau), and amyloid-beta (Aβ), as well as the total Digital Cognitive Biomarker (DCB) score, was assessed using Receiver Operating Characteristic (ROC) curve analysis. AUC values were compared to evaluate the diagnostic accuracy of each biomarker. Multinomial logistic regression analysis was conducted to examine the relationship between the DCB Total score and the diagnostic groups (cognitively normal,

mild cognitive impairment, and Alzheimer's dementia), with the cognitively normal group serving as the reference category. The model's goodness-of-fit and pseudo R-Square values were calculated to evaluate the model's performance. The software IBM SPPS Statistics was used to perform all statistical analyses.

RESULTS

Demographics and Descriptive Analysis

Demographic characteristics are found in Figures 1 and 2. There were 2,258 subjects in this database, with 10,398 assessments. The study sample included a total of 2,278 individuals, of whom 47% (n=1,069) were female. The participants' average age at the beginning of the study was 73.05 years, with a standard deviation of 7.27 years. At the start of the study, 819 participants (36%) were found to have normal cognitive function (CN), 1,021 (45%) had mild cognitive impairment (MCI), and 388 (17%) were diagnosed with Alzheimer's dementia (AD). All scores for each assessment were averaged over multiple visits resulting in N=775, among which 553 patients were diagnosed AD+ and 222 were normal. The descriptive analysis of the data in shown in Table 1. As anticipated, noteworthy variations in CSF Aβ, p-tau, and t-tau levels, as well as DCB scores, were found among the three diagnostic categories. Individuals with AD exhibited the lowest levels of CSF Aβ, the highest levels of CSF t-tau and p-tau, and lower DCB sub-scores compared to the other groups.

Biomarker	CN	MCI	AD
CSF Aβ, mean (SD), pg/ml	205.20 (55.65)	163.07 (51.29)	139.32 (35.89)
CSF p-tau, mean (SD), pg/ml	28.24 (16.28)	37.06 (21.45)	43.49 (20.30)
CSF t-tau, mean (SD), pg/ml	73.59 (30.56)	102.61 (57.01)	120.43 (60.89)
N1, mean (SD)	0.4587 (0.07)	0.3438 (0.10)	0.2338 (0.10)
N2, mean (SD)	0.4186 (.11)	0.4370 (0.10)	0.3946 (0.10)
N3, mean (SD)	0.5965 (0.08)	0.5095 (0.10)	0.4549 (0.10)
N4, mean (SD)	0.2570 (0.06)	0.2444 (0.07)	0.2382 (0.07)
R1, mean (SD)	0.3417 (0.05)	0.3355 (0.05)	0.3369 (0.06)
R2, mean (SD)	0.8458 (0.06)	0.7893 (0.08)	0.7332 (0.09)
R3, mean (SD)	0.6709 (0.06)	0.5944 (0.09)	0.5260 (0.08)
M1, mean (SD)	0.8065 (0.06)	0.7294 (0.07)	0.6341 (0.10)
M2, mean (SD)	0.8622 (0.05)	0.7526 (0.10)	0.6147 (0.13)
M3, mean (SD)	0.5993 (0.07)	0.4785 (0.10)	0.3552 (0.08)
DCB Total, mean (SD)	5.7898 (0.36)	5.0938 (0.49)	4.5583 (0.43)

Table 2. Descriptive Analysis. CN is Cognitively Normal, MCI is Mild Cognitive Impairment, AD is Alzheimer's Disease

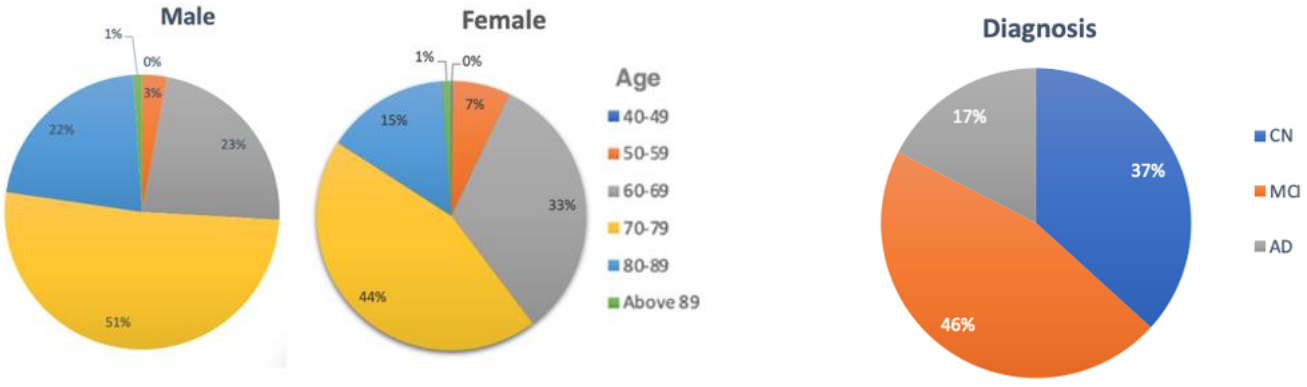

Figure 2. Pie charts of Age, Gender, and Diagnostic group

Correlations of DCBs with core CSF Biomarkers

The paired Pearson correlation coefficient analysis revealed significant associations between digital cognitive biomarkers (DCBs) and classic Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarkers (Aβ, t-tau, and p-tau) in the overall sample of 2,258 subjects with 10,398 assessments. Table 3 presents a summary of Pearson's correlation coefficients (r) between CSF biomarkers and DCB Total scores. The correlations were significant at the 0.01 level (2-tailed) for all three CSF biomarkers.

DCB	Aβ	t-tau	p-tau
N1	0.465**	-0.438**	-0.317**
N2	0.262**	-0.248**	-0.076**
N3	0.367**	-0.279**	-0.187**
N4	0.158**	-0.031*	0.004
R1	0.017	0.006	-0.077**
R2	0.426**	-0.406**	-0.287**
R3	0.457**	-0.421**	-0.260**
M1	0.466**	-0.429**	-0.295**
M2	0.470**	-0.423**	-0.294**
M3	0.499**	-0.451**	-0.295**
DCB Total	0.492**	-0.436**	-0.288**

Table 3. Summary of Pearson's Correlations Coefficients (r) between CSF Biomarkers and DCB. ** Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed).

When examining the relationship between DCB Total and CSF biomarkers within each diagnostic group (cognitively normal, mild cognitive impairment (MCI), and AD), separate paired Pearson correlation coefficient analyses showed significant associations as well. Table 4

provides a summary of Pearson's correlation coefficients (r) between CSF biomarkers and DCB Total scores per diagnostic group, with correlations significant at the 0.01 level (2-tailed).

These results suggest that DCB Total scores are significantly associated with classic AD CSF biomarkers (Aβ, t-tau, and p-tau) in the overall sample and within each diagnostic group. This indicates that digital cognitive biomarkers could potentially serve as a valuable tool in predicting and tracking Alzheimer's disease progression.

CSF Biomarker	CN DCB Total	MCI DCB Total	AD DCB Total
Aβ	0.316**	0.320**	0.217**
t-tau	-0.225**	-0.298**	-0.120**
p-tau	-0.179**	-0.240**	-0.138**

Table 4. Summary of Pearson's Correlations Coefficients (r) between CSF Biomarkers and DCB Total per diagnostic group. ** Correlation is significant at the 0.01 level (2-tailed).

Diagnostic Utility of DCBs in AD

Effect sizes of the differences between the two groups in each domain of DCB were calculated using Cohen's d. The analysis revealed significant differences between the AD+ and NORMAL groups across most of the domains of DCB. It is common to interpret effect sizes using benchmarks that classify them as small (d = 0.2), medium (d = 0.5), and large (d = 0.8) (Cohen, 1988).

Domain	Effect Size (Cohen's d)	Effect Size Interpretation	p-value
N1	1.78	Large	<0.001**
N2	0.73	Medium	<0.001**
N3	1.39	Large	<0.001**
R1	0.22	Small	0.01
R2	1.34	Large	<0.001**
R3	1.63	Large	<0.001**
M1	1.58	Large	<0.001**
M2	1.62	Large	<0.001**
M3	1.98	Large	<0.001**
DCB Total	1.87	Large	<0.001**

Table 5. Summary of Effect Sizes (Cohen's d) and interpretations between AD+ and Normal groups. ** Correlation is significant at the 0.01 level (2-tailed).

The results indicated large effect sizes in most DCB domains (N1, N3, R2, R3, M1, M2, and M3), with Cohen's d values ranging from 1.34 to 1.98 ($p < 0.001$), suggesting substantial differences between the AD+ and NORMAL groups. Moderate effect sizes were observed in N2 (Cohen's $d = 0.73$, $p<0.001$). In contrast, R1 showed a small effect size (Cohen's $d = 0.22$, $p<0.01$),. Importantly, the combined DCB score demonstrated a large effect size (Cohen's $d = 1.87$, $p<0.001$), suggesting that the composite measure effectively distinguishes between individuals with Alzheimer's disease and cognitively normal individuals. These findings support the utility of the combined DCB score as a diagnostic and research tool in Alzheimer's disease studies, as it demonstrates both large effect sizes and substantial differences between the AD+ and NORMAL groups.

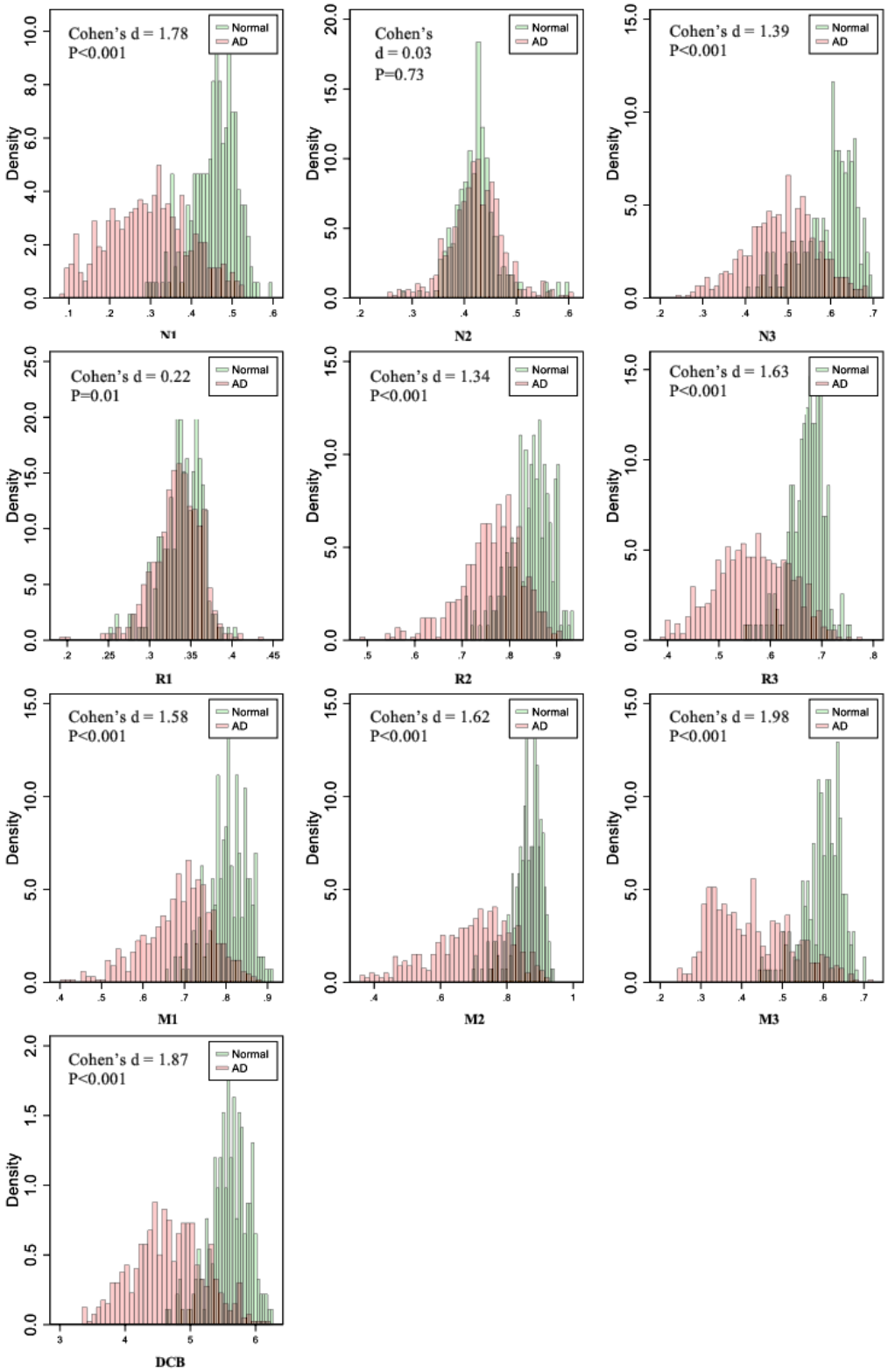

Figure 3. Histogram graphs visualizing the difference between AD (red) and normal (green) in each domain of DCB, and the combined DCB score.

In addition to the effect sizes calculated using Cohen's d, we assessed the diagnostic accuracy of each DCB domain separately and the combined DCB score for Alzheimer's disease using Receiver Operating Characteristic (ROC) curve analysis. The area under the ROC curve (AUC) values were calculated to provide a measure of diagnostic accuracy. The AUC values range from 0.5 to 1, where a higher AUC value indicates better diagnostic accuracy. If the AUC value is 0.5, it means the model is not better than random chance at making predictions. Values closer to 1 indicate better discrimination between AD+ and NORMAL groups (Hajian-Tilaki, 2013). The AUC values for each domain and the combined DCB score were as follows: N1 (0.851), N2 (0.737), N3 (0.729), N4 (0.562), R1 (0.475), R2 (0.801), R3 (0.838), M1 (0.848), M2 (0.850), M3 (0.883), and DCB total (0.869). The AUC values indicate that several domains (N1, N2, N3, R2, R3, M1, M2, and M3) exhibited good diagnostic accuracy, with AUC values ranging from 0.729 to 0.883. In contrast, N4 and R1 showed poor diagnostic accuracy, with AUC values of 0.562 and 0.475, respectively. Importantly, the combined DCB score showed good diagnostic accuracy (AUC = 0.869), suggesting that the composite measure effectively differentiates between individuals with Alzheimer's disease and cognitively normal individuals. The sensitivity and specificity of the combined DCB score were 0.837 and 0.865, respectively, indicating a high true positive rate and a low false positive rate for AD diagnosis. These results further support the use of the combined DCB score as a valuable diagnostic and research tool in Alzheimer's disease studies, as it demonstrates both high diagnostic accuracy and strong ability to differentiate between the AD+ and normal groups.

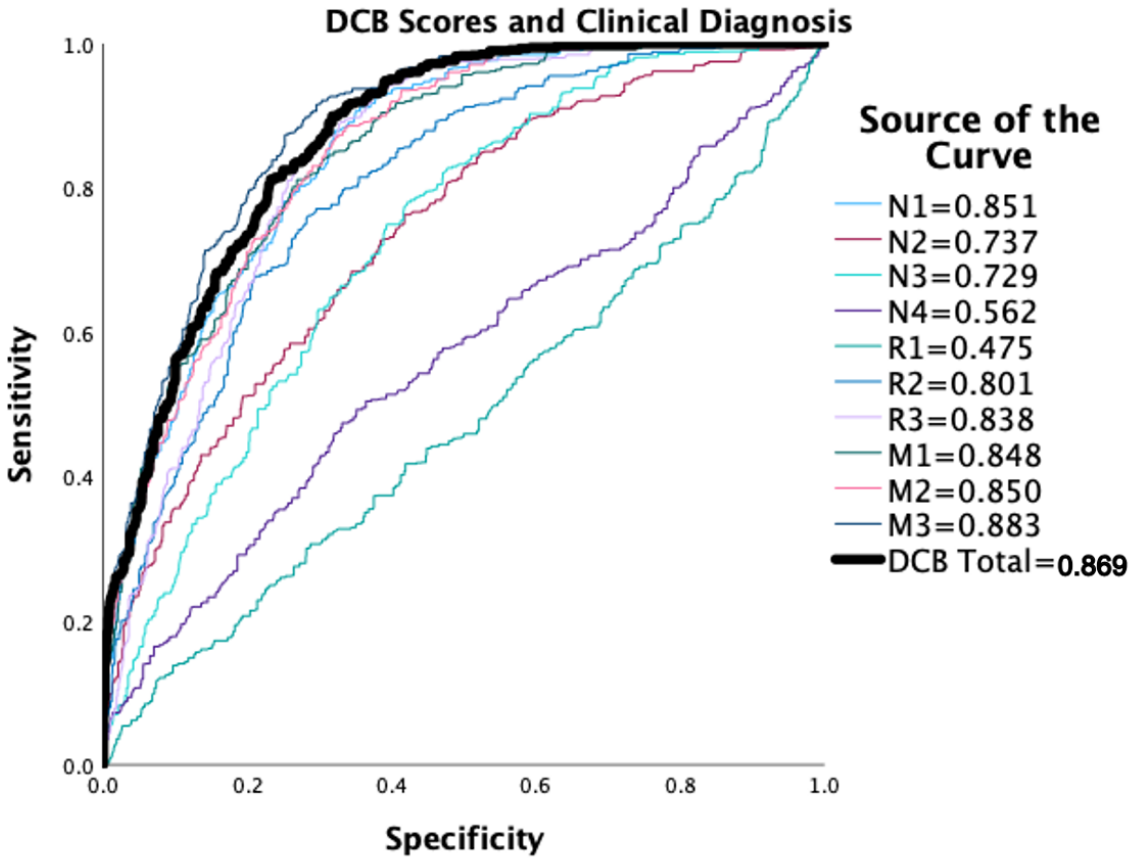

Figure 4. ROC graph showing the accuracy of AD diagnosis by each DCB domain separately, and by the combined DCB score. All scores were averaged over multiple visits.

The maximum K-S metric and associated cutoff values were also used to determine the optimal threshold for distinguishing between AD+ and normal. The K-S statistics and cutoff values provide insights into the performance of DCBs as classifiers for distinguishing between patients with varying cognitive decline levels and healthy elderly controls. The M3 and DCB Total cutoff values demonstrate the strongest classification capabilities, reinforcing their potential as noninvasive diagnostic tools for AD.

DCB	Max K-S	Cutoff
N1	0.558	0.3272
N2	0.345	0.4417
N3	0.358	0.5111
N4	0.143	0.2166
R1	0.042	0.3021
R2	0.477	0.7783
R3	0.566	0.5940
M1	0.542	0.7089
M2	0.548	0.7459
M3	0.621	0.4311
DCB Total	0.582	5.1261

Table 6. DCB maximum Kolmogorov-Smirnov (K-S) metric and the associated cutoff values.

Comparing DCB Predictability to Gold Standard CSF Biomarkers

We assessed the diagnostic accuracy of cerebrospinal fluid (CSF) biomarkers, namely tau, phosphorylated tau (p-tau), and amyloid-beta (Aβ), as well as the total Digital Cognitive Biomarker (DCB) score for distinguishing between Alzheimer's disease (AD) patients and cognitively normal (CN) individuals. The diagnostic accuracy was evaluated using Receiver Operating Characteristic (ROC) curve analysis, and the Area Under the Curve (AUC) values were compared. For the CSF biomarkers, the AUC values were as follows: tau (AUC = 0.671), p-tau (AUC = 0.681), and Aβ (AUC = 0.717). Among these biomarkers, Aβ showed the highest diagnostic accuracy in distinguishing AD+ from NORMAL individuals. However, the total DCB score demonstrated a notably higher diagnostic accuracy, with an AUC value of 0.869. Thus,

with this sample, the total DCB score outperforms the CSF biomarkers in differentiating between AD+ and NORMAL participants. In conclusion, our results indicate that the total DCB score may serve as a more accurate diagnostic tool for Alzheimer's disease compared to traditional CSF biomarkers. Further research is warranted to validate these findings and explore the potential clinical utility of the DCB score in the early detection and monitoring of AD.

A **B**

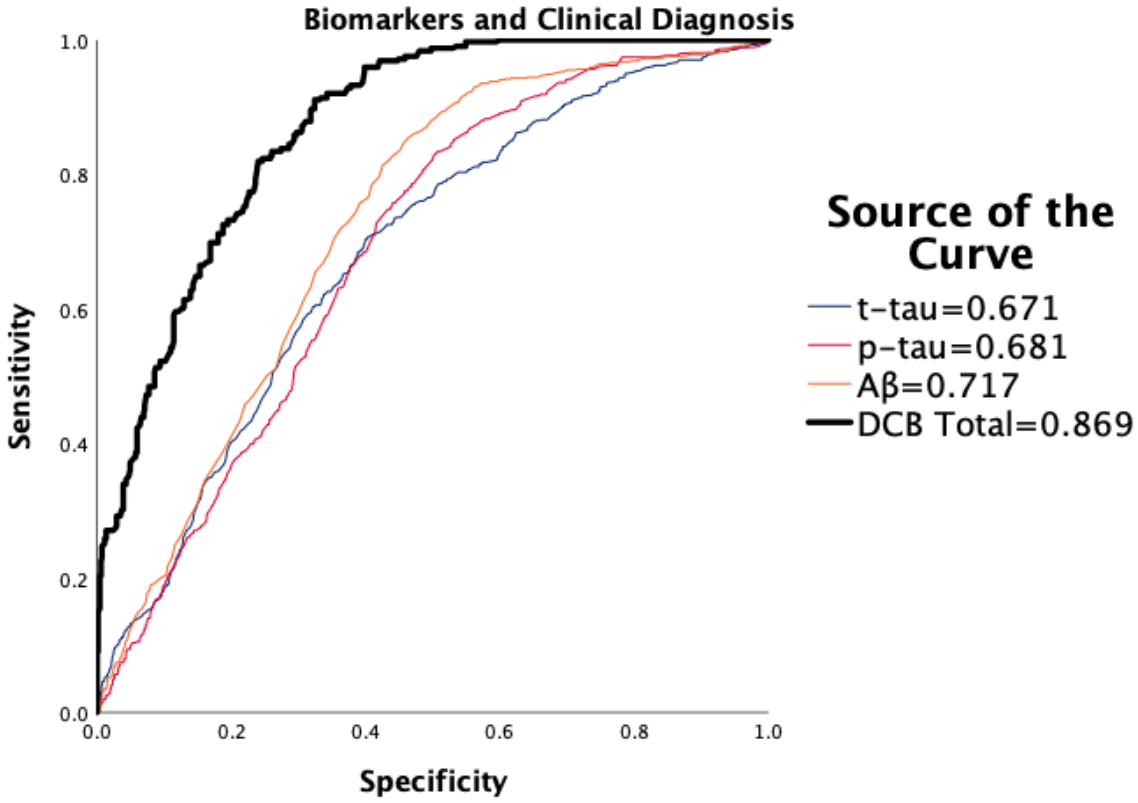

Figure 5. ROC graph showing the accuracy of differentiating between AD+ and Normal participants by CSF biomarkers and by the combined DCB score.

Predicted Probabilities of Diagnostic Groups by DCB Total Score

In order to examine the relationship between the DCB Total score and the diagnostic groups (cognitively normal, mild cognitive impairment, and Alzheimer's dementia), a multinomial logistic regression analysis was conducted. Multinomial logistic regression is a type of regression analysis used when the outcome variable has more than two categories (Liang et al., 2020). The cognitively normal group served as the reference category in the analysis. The model showed a significant fit to the data (Likelihood Ratio Test: $\chi^2(2) = 4065.42$, $p < .001$). The goodness-of-fit tests also indicated a significant fit (Pearson $\chi^2(1516) = 6946.07$, $p < .001$; Deviance $\chi^2(1516) = 6051.43$, $p < .001$). Pseudo R-Square ranges from 0 to 1, with 1 indicating a perfect fit of the model to the data. The pseudo R-Square values suggested that the model was a good fit for the data and that the DCB Total score was a useful predictor of the diagnostic group membership (Cox and Snell: .520, Nagelkerke: .587, McFadden: .340).

The parameter estimates provide more information on the relationship between the DCB Total score and the different diagnostic groups. The analysis revealed that a one-unit increase in the DCB Total score was associated with a decrease in the likelihood of having mild cognitive impairment or Alzheimer's dementia compared to the cognitively normal group. In other words, individuals with higher DCB Total scores are less likely to have mild cognitive impairment or Alzheimer's dementia than those with lower scores. The estimates from the analysis suggest that with a one-unit increase in the DCB Total score, the likelihood of having mild cognitive impairment compared to the cognitively normal group is reduced by a factor of 0.029, and the likelihood of having Alzheimer's dementia compared to the cognitively normal group is reduced by a factor of 0.002. These results indicate that the DCB Total score is a useful tool for predicting cognitive impairment and can help identify individuals who may be at risk for

developing mild cognitive impairment or Alzheimer's dementia.

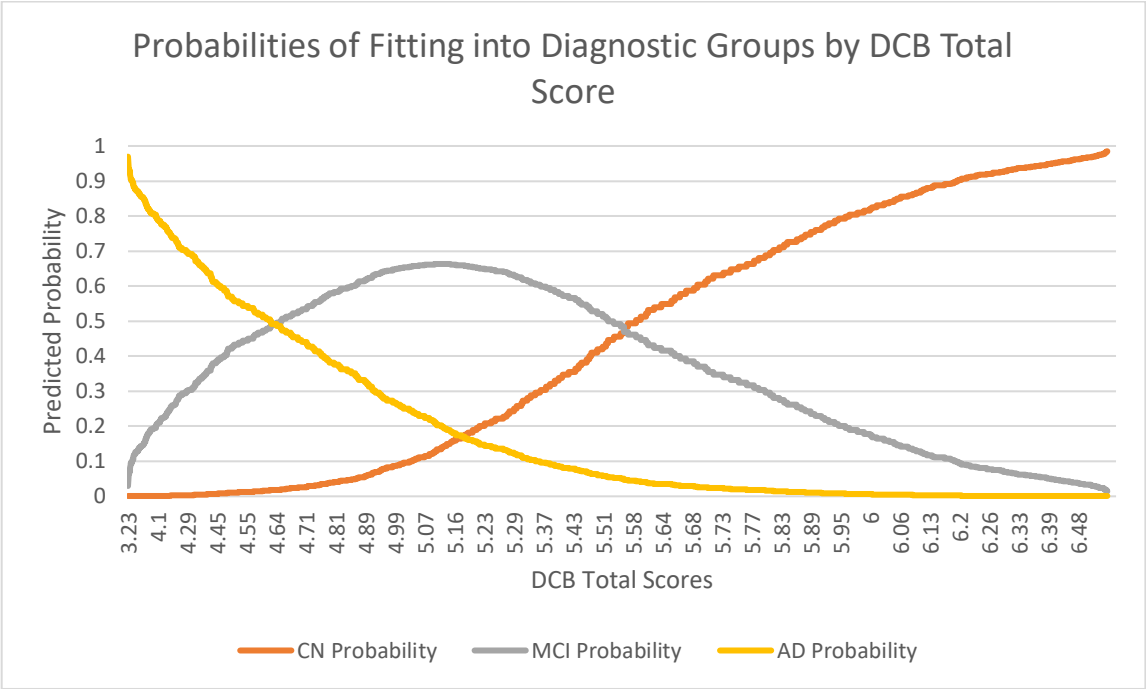

Figure 6: Predicted probabilities of diagnostic groups (CN, MCI, and AD) based on DCB Total scores. The graph illustrates the relationship between the DCB Total scores and the likelihood of an individual being classified into one of the three diagnostic groups: cognitively normal (CN), mild cognitive impairment (MCI), or Alzheimer's dementia (AD).

DISCUSSION

DCB and CSF Biomarker Correlations

The present study aimed to investigate the associations between digital cognitive biomarkers (DCBs) and classic Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarkers (Aβ, t-tau, and p-tau) in a large sample of 2,258 subjects with 10,398 assessments. Our findings revealed significant associations between DCB Total scores and all three CSF biomarkers (Aβ, t-tau, and p-tau) in the overall sample and within each diagnostic group (cognitively normal, mild cognitive impairment (MCI), and AD). These results suggest that DCBs may have the potential to serve as a valuable tool in predicting and tracking AD progression, providing support for the use of digital cognitive assessment in clinical settings.

The observed negative correlation between DCB Total scores and Aβ levels indicates that as the DCB Total scores increase, Aβ levels decrease, which is consistent with the pathological changes observed in AD. Conversely, the positive correlations between DCB Total scores and both t-tau and p-tau levels suggest that as the DCB Total scores increase, t-tau and p-tau levels also increase, reflecting the presence of neurofibrillary tangles and neuronal damage in AD.

Notably, the significant associations between DCB Total scores and CSF biomarkers were observed across all diagnostic groups, indicating that DCBs might be useful in detecting early signs of cognitive decline and monitoring disease course throughout the AD continuum. Early detection of cognitive decline is crucial for timely intervention and management of AD, as well as for the development of novel therapeutic strategies (Cummings et al., 2017; Hampel et al., 2018).

In conclusion, our study demonstrated significant associations between digital cognitive

biomarkers and classic AD cerebrospinal fluid biomarkers, suggesting the potential of DCBs as a valuable tool for predicting and tracking AD progression. These findings provide support for the use of digital cognitive assessment in clinical settings and highlight the importance of further research to establish the clinical relevance of these associations and validate the use of digital cognitive biomarkers in AD assessment and management.

Comparison of Diagnostic Utility of DCBs and CSF Biomarkers

In our study, we also sought to compare the diagnostic utility of Digital Cognitive Biomarkers (DCBs) and classic AD cerebrospinal fluid (CSF) biomarkers by examining Receiver Operating Characteristic (ROC) curves. ROC curves provide a graphical representation of the trade-off between sensitivity (true positive rate) and specificity (false positive rate) for different cut-off points of a diagnostic test. The area under the curve (AUC) serves as an overall measure of diagnostic accuracy, with an AUC of 1.0 indicating perfect discrimination and an AUC of 0.5 representing no discrimination beyond chance.

Our analysis of the ROC curves revealed that the DCBs demonstrated improved diagnostic accuracy to classic AD CSF biomarkers, as indicated by the AUC values. The combined DCB score exhibited good diagnostic accuracy (AUC = 0.869) in differentiating between AD patients and cognitively normal individuals and outperformed the diagnostic accuracy of traditional CSF biomarkers. This finding supports the idea that DCBs hold promise as an alternative or complementary diagnostic tool for Alzheimer's disease, especially considering the noninvasive nature of the DCBs. While CSF biomarkers require an invasive lumbar puncture procedure to obtain the sample, DCBs can be derived from common WLM tests, making them a cheaper and safer/risk-free option for patients. This makes DCBs a more

attractive option for routine clinical use and large-scale screening efforts.. Moreover, our examination of the ROC curves revealed potential cut-off points for DCBs that maximize both sensitivity and specificity, providing an optimal balance for early detection and accurate diagnosis of Alzheimer's disease. By utilizing these cut-off points, clinicians could potentially identify individuals at higher risk of developing AD, allowing for more targeted interventions in the preclinical stages of the disease.

It is important to note, however, that while the diagnostic accuracy of DCBs is promising, they may not be able to fully replace CSF biomarkers in all clinical scenarios. CSF biomarkers can provide direct insights into the underlying pathological processes of AD, such as amyloid-β and tau protein accumulation. In some cases, this information may be critical for distinguishing between AD and other neurodegenerative disorders with overlapping clinical presentations. Therefore, the integration of DCBs with CSF biomarkers and other diagnostic tools, such as neuroimaging, could potentially enhance the overall accuracy of AD diagnosis and offer a more comprehensive understanding of an individual's cognitive health.

There are some additional limitations to our study that should be acknowledged. Firstly, our study did not include all demographics of the patients. Therefore, it is unclear how representative our study sample is of the broader population, and whether the diagnostic accuracy of DCBs may differ across different demographic groups. Secondly, while the ADNI dataset is a valuable resource for studying AD, it may not fully capture the diversity of individuals with AD in clinical practice. Thirdly, our study only examined the diagnostic accuracy of DCBs in differentiating AD patients from cognitively normal individuals. Further research is needed to investigate the utility of DCBs in differentiating AD from other neurodegenerative disorders. Lastly, the study was conducted using data from a cross-sectional

study design, which limits the ability to draw causal inferences between DCBs and AD. Future longitudinal studies are needed to evaluate the potential of DCBs as predictive markers of disease progression and treatment response

.In conclusion, our analysis of the ROC curves suggests that DCBs have comparable diagnostic utility to classic AD CSF biomarkers, further supporting their potential as a noninvasive diagnostic tool for early detection and disease management in Alzheimer's disease. Future research should explore the optimal cut-off points for DCBs in various populations and settings, as well as the potential benefits of integrating DCBs with other diagnostic approaches to improve the overall accuracy and comprehensiveness of AD diagnosis.

Predicted Probabilities of Diagnostic Groups by DCB Total Score

Our study also aimed to investigate the connection between Digital Cognitive Biomarkers (DCBs) and the diagnostic groups of Alzheimer's disease (AD) using multinomial regression analysis. The findings revealed significant associations between the DCB Total score and the likelihood of an individual being in one of the three diagnostic groups (cognitively normal, mild cognitive impairment, and Alzheimer's dementia), showcasing the potential of multinomial regression in AD research.

The analysis demonstrated that, as the DCB Total score increased, the odds of being classified as cognitively normal increased, while the odds of being classified as having mild cognitive impairment or Alzheimer's dementia decreased. This suggests that the DCB Total score can serve as a useful diagnostic indicator of cognitive impairment in individuals. The model's pseudo R-squared values indicate that a considerable portion of the variance in diagnostic group

membership is accounted for by the DCB Total score, emphasizing the effectiveness of DCBs in predicting an individual's cognitive status. The likelihood ratio tests showed that adding the DCB Total score significantly improved the model fit, reinforcing the importance of DCBs when predicting diagnostic group membership. This result highlights the potential of multinomial regression in uncovering complex relationships between multiple categorical outcomes and predictor variables. Multinomial regression allowed us to examine the associations between the DCB Total score and the different diagnostic groups simultaneously, offering a more efficient and robust method for understanding the role of DCBs in AD diagnosis.

In conclusion, our findings show that multinomial regression analysis is useful for understanding the relationship between Digital Cognitive Biomarkers and diagnostic group membership in Alzheimer's disease research. The DCB Total score displayed strong associations with diagnostic group membership, emphasizing the potential of DCBs as a valuable diagnostic tool.

FUTURE DIRECTIONS

Our study demonstrated the potential of Digital Cognitive Biomarkers (DCBs) as a promising diagnostic tool for Alzheimer's disease, showing improved diagnostic utility to classic AD CSF biomarkers. However, there remain several areas for future research to further investigate the potential benefits of DCBs and their applications in clinical practice. One important area of interest is to investigate the ability of DCB variables to predict the time to conversion from CN to MCI, a stage that often precedes Alzheimer's dementia. By identifying individuals at higher risk of progressing from CN to MCI, clinicians may be better equipped to implement early interventions that could potentially slow the progression of the disease or mitigate cognitive decline. Longitudinal studies tracking participants with varying baseline cognitive statuses and examining the predictive power of DCBs for conversion to MCI will be critical in this regard.

It would also be valuable to explore the potential synergistic effects of combining DCBs with other diagnostic tools, such as neuroimaging and CSF biomarkers, to create a comprehensive diagnostic framework for Alzheimer's disease. A multimodal approach may yield greater accuracy and provide clinicians with a more detailed understanding of an individual's cognitive health and disease progression.

Finally, investigating the utility of DCBs in monitoring treatment response and disease progression over time could offer valuable insights for clinicians and researchers alike. By tracking the changes in DCB variables following various therapeutic interventions, researchers may be able to identify the most effective treatments for AD and better understand the underlying mechanisms through which these therapies exert their effects.

In summary, our study provides a foundation for further exploration of Digital Cognitive

Biomarkers as a noninvasive diagnostic tool for Alzheimer's disease. Future research should aim to expand upon these findings by examining the diagnostic accuracy of DCBs within distinct diagnostic groups, investigating their predictive power for conversion from CN to MCI, and exploring their applicability across diagnostic approaches. Ultimately, these efforts could pave the way for more effective early detection management of Alzheimer's disease, with the potential to reduce healthcare costs and improve patient outcomes.

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