Detection of Amyloid Status and Preclinical Alzheimer's Disease Using Cognivue Clarity®, an Adaptive Psychophysics Computerized Cognitive Battery in the Bio-Hermes Study

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KEY TAKEAWAY: **Cognivue Clarity® has great potential as an enrichment strategy for Alzheimer's disease (AD) clinical trials testing amyloid-lowering therapies as well as for AD prevention.**

BACKGROUND

With the advent of trials investigating treatment and prevention for Alzheimer's disease (AD) and mild cognitive impairment (MCI), the importance of easy and reliable screening methods to support clinical trial enrollment is clear. In the era of amyloid-lowering therapies, there is a need to identify individuals likely to have amyloid to enrich recruitment and lower costs related to amyloid PET. Further, though a subset of cognitively normal individuals has amyloid deposition (preclinical AD), to date no cognitive assessment or screening method can detect these individuals in the absence of expensive biomarkers. If there was a method to detect Preclinical AD individuals, this would greatly facilitate enrollment into prevention trials and offer a future pathway for identifying individuals for treatment of AD at the preclinical stage.

We examined the ability of Cognivue *Clarity* to discriminate True Controls (cognitively normal/amyloid negative), Preclinical AD (cognitively normal/amyloid positive) and MCI due to AD (MCI-AD, cognitively impaired/amyloid positive) from each other.

Cognivue *Clarity* is an FDA-cleared 10-minute, digital cognitive testing platform using adaptive psychophysics to capture global and domain-specific performance (Figure 1). The test generates a report that can be used by clinicians to assess cognitive status.

Figure 1. The Cognivue *Clarity* device.

DESIGN/METHODS

As part of the Bio-Hermes study, sponsored by the Global Alzheimer's Platform Foundation, Cognivue *Clarity* was administered to 1001 individuals who also had amyloid positron emission tomography (PET), plasma amyloid and tau measures, and ApoE genotyping. These individuals also underwent testing with the Mini–Mental State Examination (MMSE), Functional Activities Questionnaire (FAQ), and Rey Auditory Verbal Learning Task (RAVLT). Cognivue *Clarity* performance was compared between (1) clinically-defined, (2) biomarker-defined, and (3) clinicopathological-defined groups. Hypothesis testing was conducted to assess the ability of Cognivue *Clarity* to differentiate between True Controls, Preclinical AD, and MCI-AD. Student t-tests or one-way analysis of variance (ANOVA) with Tukey-Kramer post-hoc tests were used for continuous data and Chi-square analyses were used for categorical data. In addition to statistical significance, effect size was calculated for ability to differentiate between True Controls, Preclinical AD, and MCI-AD, between True Controls and Preclinical AD, and between Preclinical AD and MCI-AD.

RESULTS

Individuals in the sample had a mean age of 72.0±6.7 years and 15.5±2.7 years of education. Participants were 55.9% female and 23.0% were from underrepresented groups. Among clinical groups included, 41.6% were cognitively normal, 31.1% had MCI, and 27.3% had probable AD. Following amyloid PET, 21% of cognitively normal individuals were amyloid positive while only 34% of MCI cases were amyloid-positive, leading to 297 True Controls, 95 Preclinical AD and 113 MCI due to AD cases for comparison. Sample characteristics and biomarker profiles by diagnostic group are presented in **Table 1**. Cognivue *Clarity* global scores differentiated True controls from Preclinical AD and MCI-AD and differentiated Preclinical AD from MCI-AD (p<.001). The MMSE and RAVLT were unable to distinguish True Controls from Preclinical AD.

The performance on Cognivue *Clarity* global and subtests across True Controls, Preclinical AD, and MCI-AD is presented in **Table 2**. All three groups are different from each other on Cognivue *Clarity* global and all 10 subtests (all p values <.001). On post-hoc analyses, three subtests of Cognivue *Clarity* differentiated True Controls from Preclinical AD: adaptive motor control (p=.004), visual salience (p=.008), and shape discrimination (p=.004). To further study the ability of these three tests to discriminate True Controls from Preclinical AD, a composite score of the mean of the three tests was created. The 3-test mean composite score clearly differentiated True Controls from Preclinical AD (p<.001) than Cognivue *Clarity* global score or the three individual subtests.

Table 1: Sample Characteristics and Biomarker Profiles by Diagnostic Group.

	True Controls	Preclinical AD	MCI-AD	p-value
Sample Characteristics (Mean [SD] or %)				
Age	69.5 (6.2)	72.8 (6.2)	74.3 (6.2)	<.001[b]
Sex, %F	60.9	57.9	48.7	.080
Education, y	15.8 (2.4)	15.7 (2.5)	15.9 (3.1)	.878
Ethnoracial group				.504
Non-Hispanic White	80.8	85.3	85.0	
Black	10.1	10.5	7.1	
Hispanic	7.7	2.1	7.1	
Asian	1.3	2.1	0.9	
ApoE4 carrier, %	25.2	57.9	64.6	<.001[b]
MMSE	28.4 (1.5)	28.5 (1.4)	27.0 (1.9)	<.001[c]
FAQ	0.6 (1.4)	1.0 (1.9)	4.9 (5.1)	<.001[c]
RAVLT, total recall	47.9 (13.4)	46.8 (13.8)	38.3 (10.7)	<.001[c]
GDS	1.5 (1.5)	1.5 (1.7)	2.1 (1.9)	.003[c]
Cognivue Global Score	71.9 (12.5)	68.0 (12.2)	60.1 (16.2)	<.001[a]
AD Biomarkers (Mean [SD] or %)				
Amyloid PET, SUVR	0.958 (0.06)	1.324 (0.18)	1.376 (0.21)	<.001[a]
Amyloid PET, Centiloid Level	-1.7 (13.9)	65.3 (33.1)	74.8 (37.9)	<.001[b]
Aβ42/40	0.100 (0.009)	0.091 (0.008)	0.089 (0.006)	<.001[b]
APS	16.4 (19.4)	56.1 (29.9)	59.4 (26.4)	<.001[a]
pTau217	0.171 (0.06)	0.266 (0.10)	0.356 (0.23)	<.001[a]
Aβ42/40/pTau217	0.622 (0.13)	0.388 (0.14)	0.330 (0.15)	<.001[a]
pTau181	16.2 (7.5)	22.9 (14.3)	24.1 (11.0)	<.001[b]
Aβ42/40/pTau181	0.007 (0.002)	0.005 (0.002)	0.004 (0.002)	<.001[b]

Abbreviations: AD=Alzheimer's disease; FAQ=functional activities questionnaire; MCI-AD=mild cognitive impairment due to Alzheimer's disease; MMSE=mini mental state exam; RAVLT=Rey auditory verbal learning task; GDS=geriatric depression scale; SUVR=Standardized uptake value ratio.
Post-hoc analyses:
[a] All groups different from each other.
[b] True Controls different from Preclinical AD and MCI.
[c] True Controls and Preclinical AD different from MCI.

Table 2. Cognivue *Clarity* Performance by Diagnostic Group.

	True Controls	Preclinical AD	MCI-AD	True Control vs Preclinical AD	True Control vs MCI	Preclinical AD vs MCI
Cognivue Clarity Performance (Mean [SD] or %)						
Global Score	71.9 (12.5)	68.0 (12.2)	60.1 (16.2)	.014	**<.001**	**<.001**
Cognivue Clarity Subtests[a] (Mean [SD] or %)						
Adaptive Motor Control	42.6 (15.4)	37.3 (14.8)	35.0 (16.6)	**.004**	**<.001**	.311
Visual Salience	69.9 (13.7)	65.9 (13.9)	60.4 (16.9)	**.008**	**.001**	.017
Letter Discrimination	64.8 (15.8)	61.1 (17.3)	54.8 (19.5)	.070	**<.001**	.009
Word Discrimination	65.6 (17.4)	64.5 (17.7)	55.7 (19.0)	.607	**<.001**	**<.001**
Shape Discrimination	74.6 (20.1)	67.2 (20.8)	57.4 (24.4)	**.004**	**<.001**	**.001**
Motion Discrimination	70.7 (25.1)	66.8 (25.2)	56.9 (27.4)	.197	**<.001**	.007
Letter Memory	73.7 (17.4)	69.3 (17.4)	61.4 (22.3)	.053	**<.001**	**.003**
Word Memory	79.9 (19.1)	78.0 (17.1)	67.9 (23.8)	.413	**<.001**	**<.001**
Shape Memory	71.9 (22.7)	68.7 (22.6)	62.3 (23.4)	.247	**<.001**	.050
Motion Memory	77.7 (22.2)	72.4 (25.4)	68.5 (30.0)	.075	**<.001**	.263
Cognivue Clarity Composite[b] (Mean [SD] or %)						
3-test mean	62.4 (12.6)	56.6 (12.6)	50.9 (15.3)	**<.001**	**<.001**	**.003**

Abbreviations: AD=Alzheimer's disease; MCI-AD=mild cognitive impairment due to Alzheimer's disease.
[a] p-values are significant after correction for multiple comparisons (adjusted p-value=0.005).
[b] Composed of mean of Adaptive Motor Control, Visual Salience, and Shape Discrimination.

The Cognivue *Clarity* global score and the 3-test composite score had a medium-to-large effect size (Eta squared = 0.113) to distinguish between the three groups. The individual subtests had a small-to-medium effect size. When comparing True Controls vs Preclinical AD, the Cognivue *Clarity* global score (Cohen's d=0.316) had a small-to-medium effect size while the 3-test composite score (Cohen's d=0.459) had medium effect size. Of the 10 subtests, adaptive motor control (Cohen's d=0.351), visual salience (Cohen's d=0.336) and shape discrimination (Cohen's d=0.369) had the largest effect sizes.

Table 3 demonstrates the association between Cognivue *Clarity* global score, the 3 subtests that discriminate Preclinical AD, and the 3-test composite score and AD biomarkers collected in Bio-Hermes.

Table 3: Correlation Between Cognivue *Clarity* Global, Subtests, and Composite and AD Biomarkers.

	Ab42/40	APS	SUVR	pTau217	Ab42/40/pTau217	pTau181	Ab42/40/pTau181
Cognivue Clarity Performance							
Global Score	.200	-.272	-.435	-.415	-.422	-.252	-.268
Cognivue Clarity Subtests							
Adaptive Motor Control	.125	-.205	-.303	-.294	-.289	-.205	-.194
Visual Salience	.181	-.247	-.319	-.329	-.329	-.210	-.201
Shape Discrimination	.216	-.273	-.420	-.340	-.340	-.256	-.269
Cognivue Clarity Composite[a]							
3-test mean	.218	-.296	-.433	-.400	-.400	-.269	-.276

Abbreviations: APS=Amyloid Probability Score, SUVR=standardized uptake value ratio.
Pearson r, all p-values <.001 (except adaptive motor control and Ab42/40 which is .002).
[a] Composed of mean of Adaptive Motor Control, Visual Salience, and Shape Discrimination.

Receiver operator characteristic (ROC) analyses were performed to compare ability of Cognivue *Clarity* global score, 3 subtests, the 3-test composite score to discriminate between True Controls vs Preclinical AD, and Preclinical AD vs MCI-AD (**Table 4**).

Table 4: Receiver Operator Curve Analyses.

	AUC	95%CI	p-value	Youden Index	Cut-off
Cognivue *Clarity* Performance (Pearson r)[a]					
Global Score	0.599	0.535-0.662	0.002	0.166	79.5
Cognivue *Clarity* Subtests (Pearson r)[a]					
Adaptive Motor Control	0.593	0.527-0.658	0.006	0.180	39.5
Visual Salience	0.611	0.546-0.677	0.001	0.231	69.5
Shape Discrimination	0.606	0.542-0.671	0.001	0.179	75.5
Cognivue *Clarity* Composite (Pearson r)[a,b]					
3-test mean	0.634	0.570-0.698	<.001	0.227	56.8

Abbreviations: AUC=Area under the curve; 95%CI=95% confidence interval.
[a] All p-value <0.001.
[b] Composed of mean of Adaptive Motor Control, Visual Salience, and Shape Discrimination.

CONCLUSIONS

In a large study of biomarker confirmed case of True Controls, Preclinical AD, and MCI-AD, we found that Cognivue *Clarity* was able to detect Preclinical AD while other common screening tests such as MMSE and RAVLT could not. In particular, the composite of the mean of three subtests (adaptive motor control, visual salience, and shape discrimination) was significantly different between the True Controls and Preclinical AD groups. This composite of the mean performed better than the global score or individual subtests with a greater statistical significance and larger effect size. The 3-test composite was moderately correlated with amyloid PET and two plasma biomarkers (APS, pTau217) that are highly predictive of amyloid positivity on PET. Preclinical AD was distinguished from MCI-AD by cognitive performance on the global scores and 3-test composite.

To further increase the efficiency and cost-effectiveness of screening for Preclinical AD study participants, a staged screening approach likely makes the most sense. Cognivue *Clarity* could be used to establish whether there is (a) cognitive impairment, and (b) a likelihood of amyloid presence. This could be followed by measuring a readily accessible AD biomarker such as plasma pTau217. Such a strategy would increase the likelihood of identifying a case of Preclinical AD for enriching recruitment into planned clinical trials. If current prevention trials are successful, this strategy also has great potential for getting people into treatment protocols as early as possible.

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