Development of the Snellen Memory Test (SMT):
An episodic memory test to screen for AD risk in a clinical optometry/ophthalmology setting

Jennifer Strenger, MA[1,4], Ryan Aker, BSc[2], Edmund Arthur, OD, PhD[2,3,4], Louisa I. Thompson, PhD[1,4], Paul Maruff, PhD[5], Peter J. Snyder, PhD[1,2,3], & Jessica Alber, PhD[2,3,4]

[1]Alpert Medical School of Brown University; [2] University of Rhode Island; [3]George and Anne Ryan Institute for Neuroscience; [4] Butler Hospital Memory and Aging Program; [5] Cogstate, Ltd.

Introduction

Retinal Biomarkers of Alzheimer's disease (AD)

- Retinal biomarkers are an ideal target for AD risk biomarker development: the retina shares neurobiology and neurochemistry with the central nervous system (CNS), and can be visualized using standard optometry and ophthalmology techniques.
- Retinal imaging using spectral domain optical coherence tomography (SD-OCT) is minimally invasive, cost-effective, highly accessible, and can be implemented by point-of-care clinicians in clinical optometry and ophthalmology practices.
- Because many adults over the age of 40 regularly see an eye-care professional for routine care and prescription adjustments for corrective lenses, assessment of AD risk in clinical optometry practice provides an ideal opportunity for high volume screening of large portions of the population.
- Retinal biomarkers have been identified in both symptomatic and preclinical AD (Alber et al., 2020), with most research showing that retinal nerve fiber layer (RNFL) thickness is a sensitive biomarker of neurodegeneration, but is not specific to AD
- Additional information must be collected to increase the specificity of retinal AD biomarkers for point-of-care assessment of AD risk in optometry/ophthalmology to successfully refer at-risk individuals for more invasive and expensive AD risk biomarker testing.

Episodic Memory Tests are Specific to AD

- Declines in episodic memory are one of the earliest cognitive symptoms in AD
- Targeted tests of delayed recall, such as the Free and Cued Selective Reminding Test (FCSRT), allow for great sensitivity and specificity, distinguishing AD-related episodic memory issues from those related to other conditions involving memory impairment, such as frontal-temporal dementia or depression (Buschke, 1984; Lemos et al., 2014).
- Poor performance on the FCSRT has also shown a high correlation with CSF biomarkers for AD (Rami et al., 2011; Wagner et al., 2012), and poor performance on both the FCSRT and the Rey Auditory Verbal Learning Test (RAVLT) has a high correlation with volumetric MRI scans indicating atrophy in the medial temporal lobe (Habert et al., 2011; Sánchez-Benavides et al., 2010; Sarazin et al., 2010; Moradi et al., 2016), an essential structure for episodic memory (Squire and Wixted, 2011, Jeong et al., 2015).
- Traditional neuropsychological tests are administered by trained neuropsychologists in controlled conditions – however, in order to efficiently screen large segments of the asymptomatic population, episodic memory tests must be accessible and easily to administer for point-of-care clinicians.

To address this need, we aim to develop an assessment of episodic memory to be used in combination with retinal biomarker assessment and demographic information (age, family history) when assessing AD risk in clinical optometry practice. The Snellen Eye Chart, a commonly used assessment of visual acuity in optometry, will serve as the stimulus for this episodic memory assessment.

- Pairing retinal AD risk biomarkers with a short episodic memory test sensitive to AD in clinical optometry practice would generate a non-invasive, cost-effective method of AD risk detection and referral for more invasive and expensive biomarker testing (i.e. amyloid PET, specialist evaluation)

Aims

1. To create an episodic memory test to pair with retinal biomarkers in order to better target older adults with high AD risk for early intervention and referral for specialist evaluation.
2. To identify episodic memory questions of equivalent difficulty, based on the Snellen Eye Chart, that can eventually be used as an episodic memory question pool to develop a mobile application based episodic memory test for use in clinical optometry practice.

Participants

Participants were 19 cognitively normal older adults from the Atlas of Retinal Imaging in Alzheimer's Study (ARIAS), an actively recruiting, multi-site, longitudinal study examining structural, protein-related, and angiographic retinal changes across the cognitive aging spectrum, from cognitively normal older adults to mild AD patients.

Inclusion Criteria:

- Age 55 to 80, meet inclusion criteria of one of four stratified groups:

Cognitively normal, low risk	Cognitively normal, high risk	Mild cognitive impairment (MCI)	Mild AD
- MoCA total score ≥ 26 at screening - CDR 0 at screening - No family history of AD - Non-carrier for APOE ε4 allele	- MoCA total score ≥ 26 at screening - CDR 0 at screening - No diagnosis of MCI or dementia of any type - Both family history of AD and carrier for at least one APOE ε4 gene allele	- MoCA total score ≥ 19 at screening - CDR 0.5 at screening - MCI diagnosis - Score ≤ 85 on the RBANS Delayed Memory Index (DMI) - Positive prior biomarker evidence of AD	- MoCA total score ≥ 15 and ≤ 26 at screening - CDR 1 at screening - Mild AD diagnosis - Score ≤ 85 on the RBANS Delayed Memory Index (DMI) - Positive prior biomarker evidence of AD

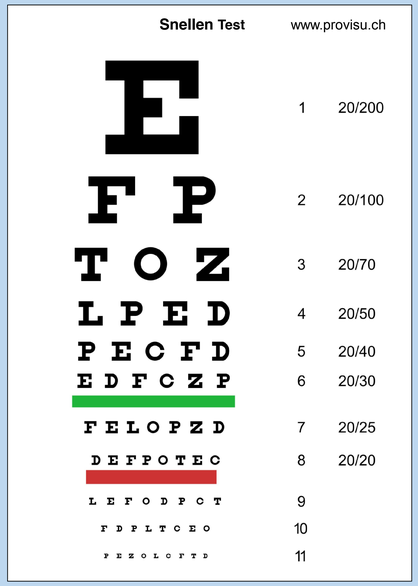
- Have a study partner willing to attend appointments

Exclusion Criteria:

- Active psychiatric disorder/hospitalization within 5 years
- Neurologic history/diagnosis that prevents compliance with ARIAS protocol
- Ocular disorder that prevents clear fundus image of retina

Demographics:

	Total Sample (N = 19) Mean (Standard Deviation)
Age	67.84 (4.87)
Education	16.16 (2.19)
Gender (%F)	68.42
MoCA (/30)	28.05 (1.51)
N per group	15 cognitively normal high risk, 4 cognitively normal low risk,



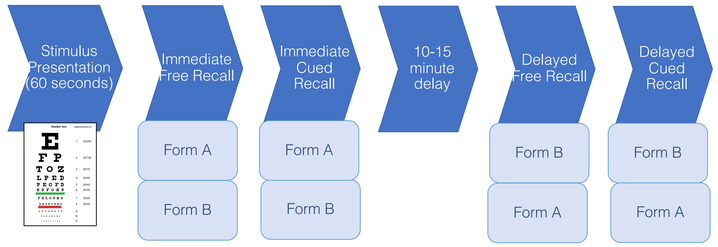
Form A

(1) Can you recall six consonants that you saw?
(2) What was the top letter?
(3) Which letter appeared most frequently?
(4) What was the last letter on the fourth row?
(5) What is the number of the row that began with the letter L?
(6) Can you recall the first letter of the third row?
(7) Can you recall the first letter of the fifth row?
(8) The letter Z appeared twice. In which row numbers did the letter Z appear?
(9) Can you recall the second row in order?
(10) Can you recall the letters that made up the fourth row?

Form B

(1) Can you recall six consonants that you saw?
(11) How many rows were between the colored bars?
(12) What number row was located above the green bar?
(13) How many times did a vowel appear?
(14) In which number row did the letter Z appear?
(15) Can you recall the first letter of the second row?
(16) Can you recall the first letter of the fourth row?
(17) Which vowels appeared on the chart?
(18) The letter D appeared in three rows. In which row numbers did the letter D appear?
(19) Can you recall the third row in order?

Methods



- Two forms (A, B) consisting of 10 questions each were developed based on the contents of the Snellen Eye Chart
- Each question had a free recall (i.e. Which vowels appeared on the chart) and a cued recall (i.e. Select the vowels you saw) version
- Participants were counterbalanced such that half received form A first, half received form B first
- Points were awarded for each correct response. Each form contained six 1-point questions, one 2-point question, one 3-point question, one 4-point question, and one 6-point question.
- In most cases, points were awarded for the correct recall of letters. For some questions which required a participant to recall multiple letters, an additional point was awarded for recall of letters in the correct order.
- Participants also completed the Free & Cued Selective Reminding Test (FCSRT) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) as part of the ARIAS protocol.

Analysis

- A mean difficulty index (DI) was calculated $\left(D_f = \frac{number\ of\ points\ earned}{Number\ of\ points\ possible}\right)$ for each of the 19 questions
- Confidence intervals were calculated for recall each condition (Immediate Free Recall, Immediate Cued Recall, Delayed Free Recall, and Delayed Cued Recall).
- Questions with DIs falling below the lower bound of the CI in the immediate cued recall condition ("too difficult") or above the upper bound of the CI in the delayed free recall condition ("too easy") were excluded from analysis. After exclusions, 10 questions remained with approximately equivalent difficulty.
- New total scores for Immediate Free and Cued Recall and Delayed Free and Cued Recall were calculated using only the results of the 10 remaining questions.
- To compare the SMT to gold standard memory measures, partial correlations, controlling for age and sex, were conducted comparing:
  1. Delayed free recall on the SMT and RBANS Delayed Memory Index (DMI)
  2. Delayed cued recall on the SMT and RBANS DMI
  3. Delayed free + delayed cued recall on the SMT and RBANS DMI
  4. Immediate free recall on the SMT and immediate free recall on the FCSRT
  5. Delayed free recall on the SMT and delayed free recall on the FCSRT.
- *Pearson's r* was used when test scores were normally distributed, and the non-parametric alternative *Spearman's rho* was used when assumptions of normality were violated.

Results

		Immediate Free Recall (IFR)	Immediate Cued Recall (ICR)	Delayed Free Recall (DFR)	Delayed Cued Recall (DCR)
	Mean difficulty index (DI)	0.55	0.59	0.58	0.62
95% confidence interval (CI)	Upper bound	0.68	0.69	0.72	0.75
	Lower bound	0.42	0.49	0.45	0.49
	Cut-off lower bound	<0.42	<0.49	<0.45	<0.49
	Cut-off upper bound	>0.68	>0.69	>0.72	>0.75
Note	Close to one = easiest				
	Min DI	0.00	0.20	0.00	0.10
	Max DI	1.00	1.00	1.00	1.00

Nine questions were excluded due to being outside the CI in the difficulty index analysis

- Questions 1, 2, 12, and 17 were excluded for being too easy on delayed free recall
- Questions 4, 6, 7, 15, 16 were excluded for being too difficult on immediate cued recall
- Questions 3, 5, 8, 9, 10, 11, 13, 14, 18, and 19 remained after exclusions

Questions With Approximately Equivalent DI Remaining After Disqualifications (N=10)

Q#	IFR	ICR	DFR	DCR	Questions
3	0.82	0.73	0.67	0.67	Which letter appeared most frequently?
5	0.36	0.55	0.44	0.44	What is the number of the row that began with the letter L?
8	0.55	0.50	0.72	0.78	The letter Z appeared twice. In which row numbers did the letter Z appear?
9	0.58	0.61	0.70	0.74	Can you recall the second row in order?
10	0.59	0.75	0.53	0.75	Can you recall the letters that made up the fourth row?
11	0.30	0.90	0.50	0.70	How many rows were between the colored bars?
13	0.40	0.70	0.20	0.20	How many times did a vowel appear?
14	0.50	0.50	0.60	0.70	In which number row did the letter Z appear?
18	0.63	0.50	0.70	0.70	The letter D appeared in three rows. In which row numbers did the letter D appear?
19	0.40	0.68	0.65	0.73	Can you recall the third row in order?

Adjusted Scores on SMT (/21)

	Mean Score	SD	Range
IFR	5.80	3.17	1-11
ICR	7.00	2.03	4-11
DFR	6.37	2.14	2-9
DCR	7.21	1.78	4-11

Partial Correlation Matrix (controlling for age, sex)
Correlation coefficient, p value

	RBANS DMI (N=19)	FCSRT IFR (N=8)	FCSRT DFR (N=8)
SMT IFR		.099, .832	
SMT ICR			
SMT DFR	.134, .608		.233, .615
SMT DCR	.116, .658		
SMT DFR + DCR	.139, .595		

- Floor effect on mean total scores of 10 questions of approximately equivalent difficulty
- No significant partial correlations (all p>.10) controlling for age and sex between SMT and other gold-standard memory measures (FCSRT, RBANS).

Discussion

- Lack of correlation with gold standard memory measures could be due to:
  a) restricted range in RBANS and FCSRT scores in our cognitively normal sample
  b) small sample size (N=19 for RBANS, N=8 for FCSRT)
- Floor effects on mean total scores in all recall conditions show current iteration of the test is too difficult
- Moving forward, we will design the SMT to be sensitive to the earliest signs of episodic memory decline in cognitively normal older adults
- New free recall format will include recalling all letters seen on Snellen chart after stimulus presented for 1 minute
- Cued recall will be a forced choice recognition paradigm: participants will be presented with pairs of letters (1 target, 1 lure) and asked to choose which letter they saw on the Snellen Chart
- Research shows preclinical AD participants show subtle longitudinal decline in tests of episodic memory (Alber et al., 2020; Papp et al., 2019; Buckley et al., 2019)
- Future work will examine longitudinal changes in SMT scores
- Future goal: creation of an AD risk algorithm mobile application (including SD-OCT retinal biomarkers, SMT, and demographic factors) for use in point-of-care clinical optometry setting and referral of high risk cognitively normal older adults for more invasive, expensive AD risk biomarker assessment