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Brief Report

Memory for Semantically Related Objects Differentiates Cognitively Unimpaired Autosomal Dominant Mutation Carriers from Non-Carrier Family Members

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Abstract

Early cognitive changes due to Alzheimer's disease (AD) include difficulties in semantic access and working memory. Using a computerized cognitive test developed by our group, called the Memory for Semantically Related Objects test (MESERO), we evaluated if cognitively unimpaired carriers of an autosomal dominant AD (ADAD) mutation performed worse on this test than non-carrier family members. 35 cognitively unimpaired ADAD mutation carriers and 26 non-carrier family members from a Colombian ADAD cohort took the MESERO on a laptop computer. Cognitively unimpaired ADAD carriers had significantly worse MESERO total scores than non-carrier family members, driven by worse performance in semantically-related object sets; group performances did not differ on semantically unrelated object sets. Findings suggest that MESERO performance may be sensitive to subtle cognitive changes associated with AD. Future MESERO research should examine performances between healthy older adults and people at risk for sporadic AD.

Key words: Cognition, neuropsychology, Alzheimer's disease, working memory.

Introduction

The prevalence of undetected neurodegenerative disorders, such as Alzheimer's disease (AD), is a growing international public health problem (1). Within this context, the development of unique and innovative technological approaches to detecting and tracking cognitive changes occurring early in conditions like AD is necessary. One such approach is the development of remotely administered computerized cognitive assessments (2). There have been several computerized cognitive tests that have been created and validated over the last decade (3–9), though notably the study and validation of computerized cognitive tests in culturally diverse samples needs significant attention moving forward (10). Remotely administered cognitive assessments, however, provide a unique opportunity to easily gather information from patients or research participants on their personal devices, thereby potentially creating an avenue to improve the accessibility of cognitive assessments to historically marginalized and underserved populations.

Previous research has suggested that semantic memory is an aspect of cognition that is impacted early in AD (11, 12), with subordinate semantic concepts being vulnerable to disruption (i.e., "blocks," "doll," "action figure"), whereas access to superordinate semantic structures (i.e., the category of "toys") is preserved (13). People with AD often have issues forming semantic associations (14), and greater difficulty with forming semantic associations on a memory test has been demonstrated to be related to elevated levels of AD biomarkers (15). From a clinical perspective, the breakdown of hierarchical semantic concepts may present as anomia, wherein a person with AD may be able to identify the superordinate category of an item on a confrontation naming test (e.g., a toy) but cannot generate the subordinate object's name (e.g., a doll). The intersection of semantic degradation with working memory may provide a potentially useful avenue for further working memory test development to identify people at risk for the AD clinical syndrome.

Previously, our group developed and piloted the Memory for Semantically Related Objects (MESERO) test (16). Prior to the SARS-COV-2 (COVID-19) pandemic, we reported initial acceptability and feasibility data (e.g., accuracy scores and reaction time) for the MESERO in a sample of healthy, young Spanish-speaking adults living in Spain and Colombia (16). In the present study, we examined whether MESERO performance differs between cognitively unimpaired carriers of an autosomal dominant AD (ADAD) mutation and non-carrier family members from the Colombian Presenilin1 (*PSEN1*) E280A kindred cohort (see Fuller et al., 2019 for more information about this ADAD cohort (17)). We hypothesized that cognitively unimpaired ADAD mutation carriers – who were more than a decade

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younger than the median age of clinical symptom onset for this cohort (18) – would have a significantly worse overall total score on the MESERO relative to non-carrier family members, and that this worse performance on the MESERO would be driven by significantly worse performance on semantically-related object conditions, in particular, given increased sematic interference (11, 12). We also anticipated that cognitively unimpaired ADAD mutation carriers would have slower reaction times on the MESERO relative to non-carrier family members.

Methods

Study Design and Participants

Approval for the present study was obtained from the Mass General Brigham Institutional Review Board (Boston, MA) and from the University of Antioquia Ethics Committee in Medellín, Colombia. Participants provided written informed consent prior to completion of study procedures. All data were acquired by investigators who were masked to the participants' genetic status.

A total of 83 Colombian individuals from the *PSEN1* E280A kindred cohort (37 non-carriers; 46 carriers [including 5 meeting criteria for mild cognitive impairment [MCI] due to ADAD]) took part in this research study. 17 participants (11 non-carriers, 6 cognitively unimpaired ADAD mutation carriers) were excluded from the initial sample due to taking the MESERO on a smartphone or tablet device while they were not in the clinic (i.e., they were likely taking the test at home). The resultant 66 participants took the MESERO on an internet browser (e.g., Chrome) on Windows computer in the presence of a study team member during a research visit to the clinic at the University of Antioquia or during their research visit to Massachusetts General Hospital as part of the ongoing COLombia-BOSton (COLBOS) longitudinal biomarker study of ADAD.

MESERO and other cognitive tests

The procedures of the computerized MESERO and its delayed matching to sample paradigm (19) have been described elsewhere in detail (16). Briefly, during the MESERO test takers are shown 80 sets of objects at differing loads (i.e., 4 vs. 6 objects in a set). The "semantic relatedness" of the objects is manipulated between related objects (i.e., all objects belonging to a superordinate semantic category, [e.g., modes of transportation]) and unrelated objects. The MESERO was developed with the idea that the inability to access superordinate categorical processes in people at elevated risk for AD (and other disorders) could result in difficulties on the MESERO (16). Specifically, it is thought that at higher task loads (e.g., 6 objects vs. 4 objects) and when objects are semantically related individuals may have more difficulty creating distinct working memory representations of related objects. Conversely, in unrelated object sets, a lack of access to subordinate categorical characterization may not interfere with task performance in individuals at elevated AD risk because the superordinate characterization (e.g., "fruit" for "apple," "clothes" for "shirt") would be sufficient for forming distinct mental representations requisite for encoding and maintaining successful working memory representations. The MESERO program automatically scores the accuracy of participant responses to the yes/no recognition questions presented in the delayed matching to sample paradigm (out of 80 possible points) and calculates average reaction time (in milliseconds) for four main groups of items (4 semantically related items; 4 semantically unrelated items; 6 semantically related items; and 6 semantically unrelated items).

In the present study, participants were provided instructions and test questions in their native and primary language (Spanish). One notable change from the first version of the MESERO (16) is that the current study used an updated version of the MESERO (i.e., MESERO v. 2.0) that used colorized images relative to the black-and-white images in the original version of the MESERO. These images were carefully chosen by a team consisting of study team members who were from various countries (i.e., Colombia, the United States, Brazil, Turkey, and South Korea); the cross-cultural appropriateness of each image was also discussed by this team. Data from MESERO v. 2.0 is also more easily stored and exported data from an encrypted cloud drive relative to the original version of the test where study staff had to take a screenshot of the results page and manually input results to the database. Other aspects of the MESERO (e.g., size of images, timing of the stimuli, number of trials) remained consistent with the original version of the task. Participants in this study also took the Mini-Mental State Examination (MMSE) (20) and were evaluated by trained clinicians using the Functional Assessment Staging Tool (FAST) (21) during their research visit to determine their cognitive status (i.e., cognitively unimpaired vs. MCI).

Statistical analysis

Differences on demographic factors between cognitively unimpaired ADAD mutation carriers and non-carrier family members were evaluated with independent samples t-tests (for continuous variables) and chi-square tests (for nominal variables). For these t-tests, Cohen's d was calculated as a standardized effect size. Due to the skewness of MESERO data, differences between cognitively unimpaired ADAD mutation carriers and non-carrier family members on MESERO accuracy and reaction time were evaluated with the Mann-Whitney test. Effect sizes for Mann-Whitney tests (r) were calculated using a procedure which takes divides the standardized test statistic (Z) of the Mann-Whitney test by the square root of the numbers of pairs in the test. The

Table 1. Sample Descriptive Data

	Non-Carrier (n=26)	Cognitively Unimpaired PSEN1 E280A Carrier (n=35)	PSEN1 E280A Carrier with MCI due to ADAD (n=5)	Test statistic, significance, and effect size
Age (years)	36.68 (6.52)	30.46 (5.28)	47.60 (1.67)	t=3.92, p<.001, d=1.01***
Education (years)	11.42 (4.30)	11.14 (3.39)	7.00 (2.83)	t=0.29, p=.39
MMSE	28.77 (1.14)	28.06 (1.19)	22.60 (4.34)	t=2.36, p=.01, d=0.61*
FAST (2 < # < 5)	0	0	5	n/a
Sex (males:females)	11:15	11:24	1:4	χ^2=0.77, p=.38

*p<.05, **p <.01, ***p <.001; Abbreviations: PSEN1 = Presenilin1; FAST = Functional Assessment Staging Tool; MMSE = Mini-Mental State Exam; MCI = mild cognitive impairment; ADAD = autosomal dominant Alzheimer's disease.

Table 2. MESERO Task Performance (Accuracy) and Reaction Time in the Colombian Kindred

	Non-Carrier (n=26)	Cognitively Unimpaired PSEN1 E280A Carrier (n=35)	PSEN1 E280A Carrier with MCI due to ADAD (n=5)	Test statistic, significance, and effect size
MESERO Total Score (out of 80)	73.46 (5.67)	70.77 (6.51)	64.60 (8.68)	U=312, p=.04, r=.27*
MESERO Related Trials Sub-Score (out of 40)	35.77 (2.89)	33.91 (4.15)	31.60 (5.27)	U=312.5, p=.04, r=.27*
MESERO Unrelated Trials Sub-Score (out of 40)	37.69 (3.31)	36.85 (3.48)	33.00 (3.53)	U=357 p=.15, r=0.19
4-Item Object Load Score (out of 40)	37.31 (3.18)	35.54 (4.19)	32.40 (5.32)	U=300.5, p=.02, r=0.29*
6-Item Object Load Score (out of 40)	36.15 (2.69)	35.23 (3.04)	32.20 (3.42)	U=366.5, p=.19, r=0.17
Average RT (ms)†	2817.17 (1039.54)	2578.94 (793.71)	3563.70 (1197.65)	U=392 p=.36
Average RT Related Trials (ms) †	2856.27 (1137.84)	2623.86 (914.46)	3524.98 (1270.83)	U=392 p=.36
Average RT Unrelated Trials (ms) †	2778.07 (1039.55)	2534.03 (734.08)	3602.43 (1128.58)	U=393, p=.37
Average RT 4-Item Trials (ms) †	2636.13 (973.95)	2483.92 (864.50)	3445.37 (1005.44)	U=399, p=.56
Average RT 6- Item Trials (ms) †	2998.21 (1178.13)	2673.96 (812.29)	3682.03 (1427.50)	U=373, p=.33

*p<.05, **p <.01, ***p <.001; Abbreviations: PSEN1 = Presenilin1; MESERO = Memory for Semantically Related Objects Test; MCI = mild cognitive impairment; ADAD = autosomal dominant Alzheimer's disease; RT = reaction time; ms = milliseconds; † RT analyses were conducted after removing one non-carrier who had a very large average RT that was >10000 ms.

interpretation of this Mann-Whitney effect size (r) is as follows: 0.1 = small effect 0.3 = moderate effect; and 0.5 = large effect (for discussion see https://www.sheffield.ac.uk/polopoly_fs/1.714552!/file/stcp-marshall-MannWhitS.pdf). For statistical analyses of reaction time data, one non-carrier had a large average reaction time (>10000 milliseconds [ms]) and was accordingly excluded from the reaction time analyses. For all analyses, a critical value of .05 was set as the threshold for statistical significance.

Results

Table 1 lists the demographic information for the sample in this study. Non-carriers were significantly older and had better MMSE scores on average than cognitively unimpaired ADAD carriers. Data from the *PSEN1* E280A mutation carriers who met criteria for MCI are included in Table 1 for comparison purposes.

On the MESERO total score, cognitively unimpaired ADAD mutation carriers had significantly worse scores on average relative to non-carrier family members (Table 2), with the difference approaching the suggested cutoff of r=0.3 for a moderate effect size. Cognitively unimpaired carriers, in particular, performed significantly more poorly than non-carriers on the trials of the MESERO when items were semantically related; the groups did not differ significantly on the MESERO trials where objects were not semantically related (Table 2). Additionally, the cognitively unimpaired carriers performed significantly more poorly than non-carriers on trials with 4-items in the encoding set, but not when 6-items were in the encoding set (Table 2). No statistically significant differences were seen between the cognitively unimpaired carriers and non-carriers on reaction time variables from the MESERO (Table 2).

Discussion

In the current study, we present data from a study of cognitively unimpaired individuals with an ADAD mutation (*PSEN1* E280A) and non-carrier family members who took a computerized version of the MESERO. The MESERO was designed as a remote digital cognitive assessment that intends to evaluate declines in visual working memory and its intersection with semantic processing (16), as these two cognitive functions are believed to be impacted early by neurodegenerative conditions like AD (22–25). Consistent with our hypothesis, we found that cognitively unimpaired *PSEN1* E280A mutation carriers (who were on average 14 years younger than the median age of MCI for this ADAD cohort (18)) had worse overall performance on the MESERO relative to non-carrier family members.

Regardless of object load, cognitively unimpaired mutation carriers also had significantly worse accuracy on semantically-related MESERO items relative to non-carriers, but the groups did not differ on unrelated object conditions. Cognitively unimpaired mutation carriers performed more poorly than non-carriers at 4-item object, but not at 6-item load, regardless of semantic relatedness of objects, a finding that did not support our hypotheses. Cognitively unimpaired ADAD carriers also did not differ on reaction time on any of the conditions relative to non-carrier family members, which also did not support our hypotheses.

This study provides an important step in advancing our understanding of the MESERO and its potential future clinical use alongside other cognitive tests. The detection of significantly worse average performance on the MESERO total score (and, in particular, the score on related conditions) in cognitively unimpaired ADAD mutation carriers relative to non-carrier peers a decade and a half before the typical age of onset of MCI in this cohort is a remarkable finding. Notably, unlike many prior studies in this cohort (17), in the present study the sample of cognitively unimpaired carriers was on average about 5 years younger than the sample of non-carriers family members. These effect size differences between the groups on the MESERO accuracy were moderate in size (e.g., r=.27 from Mann-Whitney). Regarding raw scores, the average differences are somewhat small (e.g., the average MESERO total score in cognitively unimpaired ADAD mutation carriers is 2.69 points worse than non-carrier average score), though the fact that on average cognitively unimpaired carriers performed significantly worse on the MESERO relative to non-carrier peers supports its potential future clinical utility. Though not formally compared due to the small sample size, the ADAD mutation carriers with MCI (n=5) had an average MESERO total score that was nearly 9 points worse than the average non-carrier total score. In the current study we were constrained by the small sample size, but we anticipate that future work with this measure may reveal that MESERO scores that are departures from the ceiling scores seen in healthy individuals (e.g., non-carriers) may reflect cognitive changes seen in the preclinical and early stages of AD.

This study has limitations that should be noted. First, the overall sample size was relatively small, although the size is standard for this type of study with a single ADAD mutation (17), resulting in even smaller sub-samples that precluded more sophisticated statistical analyses. Nonetheless, we believe that providing this initial data on MESERO performance in people with a known ADAD mutation and their non-carrier family members provides critical information that will inform the future study of this cognitive test with larger samples and different populations (e.g., people with subjective cognitive decline or MCI due to sporadic AD). Additionally, while the MESERO was designed to be used on most electronic devices (e.g., personal computers, smartphones, tablets, etc.), we chose for the current study to focus on the data from the participants who took the MESERO on computers to reduce variability of the data. Future work with the MESERO should evaluate the equivalence of the MESERO across different device types, as the prevalence of smartphones and tablets in the general population is greater than personal computers (26). Understanding how individuals perform on the MESERO and other remotely administered cognitive tests on smartphone and tablets will be an essential step to advancing the accessibility of neuropsychological services to individuals historically underserved by traditional models of in-person neuropsychological assessment. Educational experiences also likely impact individuals' comfort using computers and other technologies, and education has been shown to impact the shaping of semantic concepts (27). Future work with the MESERO will need to consider the impact of formal educational experiences on task accuracy and reaction time. Another limitation is that sample of non-impaired (i.e., preclinical) ADAD mutation carriers in this study were about 5 years younger on average than their non-carrier family members. This age difference likely contributes to a weakening of the significant difference seen between groups on the MESERO total score and related trials sub-score, though we found a significant difference between the groups nonetheless (with cognitively unimpaired carriers being approximately 15 years away from the estimated age of MCI onset in this cohort (18)). The age difference may also contribute to the result wherein cognitively unimpaired carriers and non-carrier family members did not differ on reaction time on any condition of the MESERO. The effect of age on RT differences (or lack thereof) is important to consider given that older age likely corresponds to slower reaction time on this task, even in healthy individuals (see García-Magariño & Fox-Fuller et al., 2020 for discussion (16)).

A final limitation or point of debate is the degree to which these results about the MESERO indicate that working memory, semantics, or both are vulnerable in the preclinical and early periods of ADAD. Prior research in both people with sporadic AD (15) and ADAD (12) strongly supports the notion that semantic access is disrupted early in the disease process and is correlated with AD biomarkers. The semantic interaction with a working memory component may be partially or fully driving the effect seen here, especially given that performances at higher object load (6 objects) did not differ between the groups, but performance at lower object load (4 objects) was worse in preclinical ADAD carriers relative to non-carrier family members. Future work with the MESERO could include even higher object loads (e.g., 8 objects) to further evaluate potential working memory-related contributions to the MESERO differences seen between these cognitively unimpaired *PSEN1* E280A carriers and non-carrier family members. Moreover, future research with the MESERO needs to examine performance in the context of premorbid functioning and global semantic knowledge, which could

include measures like the Wechsler Adult Intelligence Scale 4th Edition (WAIS-IV) Similarities sub-test (28) and Category Fluency (Animals) (29).

In summary, in the present study we found that cognitively unimpaired ADAD mutation carriers who were on average ~14 years away from the estimated age of onset of MCI for this cohort (18) had significantly lower computerized MESERO total scores relative to non-carrier family members. The significant difference in overall MESERO total score was driven by cognitively unimpaired ADAD mutation carriers performing worse on the conditions where objects were semantically related. This first MESERO data from a group of individuals with a virtual guarantee of developing the AD clinical syndrome in mid-life (17) and non-carrier family members supports the further study and development of the MESERO as a tool that may be sensitive to subtle cognitive changes associated with Alzheimer's disease and can potentially help track disease progression in Spanish-speaking individuals at increased risk to developing dementia. Future work in larger samples should consider correlating MESERO performance with biomarkers of AD progression, such as in vivo markers of amyloid-beta or tau in the brain (30) and plasma markers of neurodegeneration (31). Evaluating how performance on this task corresponds with activation during a functional magnetic resonance imaging paradigm would also be useful to identify the brain structures and networks which underpin MESERO performance, thereby furthering our understanding of cognitive and brain systems that are disrupted in the preclinical period of AD.

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References

1. Lang L, Clifford A, Wei L, et al. Prevalence and determinants of undetected dementia in the community: a systematic literature review and a meta-analysis. BMJ Open. 2017;7(2):e011146. doi:10.1136/bmjopen-2016-011146
2. Tsoy E, Strom A, Iaccarino L, et al. Detecting Alzheimer's disease biomarkers with a brief tablet-based cognitive battery: sensitivity to Aβ and tau PET. Alz Res Therapy. 2021;13(1):36. doi:10.1186/s13195-021-00776-w
3. Dougherty Jr. JH, Cannon RL, Nicholas CR, et al. The Computerized Self Test (CST): An Interactive, Internet Accessible Cognitive Screening Test For Dementia. Journal of Alzheimer's Disease. 2010;20(1):185-195. doi:10.3233/JAD-2010-1354
4. Gur RC, Richard J, Hughett P, et al. A cognitive neuroscience-based computerized battery for efficient measurement of individual differences: Standardization and initial construct validation. Journal of Neuroscience Methods. 2010;187(2):254-262. doi:10.1016/j.jneumeth.2009.11.017
5. Papp KV, Samaroo A, Chou H, et al. Unsupervised mobile cognitive testing for use in preclinical Alzheimer's disease. Alzheimers Dement (Amst). 2021;13(1):e12243. doi:10.1002/dad2.12243
6. Possin KL, Moskowitz T, Erlhoff SJ, et al. The Brain Health Assessment for Detecting and Diagnosing Neurocognitive Disorders. Journal of the American Geriatrics Society. 2018;66(1):150-156. doi:10.1111/jgs.15208
7. Saxton J, Morrow L, Eschman A, Archer G, Luther J, Zuccolotto A. Computer assessment of mild cognitive impairment. Postgrad Med. 2009;121(2):177-185. doi:10.3810/pgm.2009.03.1990
8. Weintraub S, Dikmen SS, Heaton RK, et al. Cognition assessment using the NIH Toolbox. Neurology. 2013;80(11 Suppl 3):S54-S64. doi:10.1212/WNL.0b013e3182872ded
9. Hammers D, Spurgeon E, Ryan K, et al. Validity of a brief computerized cognitive screening test in dementia. J Geriatr Psychiatry Neurol. 2012;25(2):89-99. doi:10.1177/0891988712447894
10. Tsoy E, Zygouris S, Possin KL. Current State of Self-Administered Brief Computerized Cognitive Assessments for Detection of Cognitive Disorders in Older Adults: A Systematic Review. J Prev Alzheimers Dis. 2021;8(3):267-276. doi:10.14283/jpad.2021.11
11. Hodges JR. Memory in the dementias. The Oxford handbook of memory. Published online 2000:441-459.
12. Vila-Castelar C, Muñoz N, Papp KV, et al. The Latin American Spanish version of the Face-Name Associative Memory Exam is sensitive to cognitive and pathological changes in preclinical autosomal dominant Alzheimer's disease. Alzheimer's Research & Therapy. 2020;12(1):104. doi:10.1186/s13195-020-00671-w
13. Giffard B, Desgranges B, Nore-Mary F, et al. The nature of semantic memory deficits in Alzheimer's disease: New insights from hyperpriming effects. Brain. 2001;124(8):1522-1532. doi:10.1093/brain/124.8.1522
14. Di Giacomo D, De Federicis LS, Pistelli M, et al. The loss of conceptual associations in mild Alzheimer's dementia. J Clin Exp Neuropsychol. 2012;34(6):643-653. doi:10.1080/13803395.2012.667393
15. Grober E, Lipton RB, Sperling RA, et al. Associations of Stages of Objective Memory Impairment With Amyloid PET and Structural MRI: The A4 Study. Neurology. 2022;98(13):e1327-e1336. doi:10.1212/WNL.0000000000200046
16. García-Magariño I, Fox-Fuller JT, Palacios-Navarro G, Baena A, Quiroz YT. Visual working memory for semantically related objects in healthy adults. Rev Neurol. 2020;71(8):277-284. doi:10.33588/rn.7108.2019479
17. Fuller JT, Cronin-Golomb A, Gatchel JR, et al. Biological and Cognitive Markers of Presenilin1 E280A Autosomal Dominant Alzheimer's Disease: A Comprehensive Review of the Colombian Kindred. The journal of prevention of Alzheimer's disease. 2019;6(2):112-120.
18. Acosta-Baena N, Sepulveda-Falla D, Lopera-Gómez CM, et al. Pre-dementia clinical stages in presenilin 1 E280A familial early-onset Alzheimer's disease: a retrospective cohort study. The Lancet Neurology. 2011;10(3):213-220.
19. Paule MG, Bushnell PJ, Maurissen JP, et al. Symposium overview: the use of delayed matching-to-sample procedures in studies of short-term memory in animals and humans. Neurotoxicol Teratol. 1998;20(5):493-502. doi:10.1016/s0892-0362(98)00013-0
20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6
21. Sclan SG, Reisberg B. Functional assessment staging (FAST) in Alzheimer's disease: reliability, validity, and ordinality. Int Psychogeriatr. 1992;4 Suppl 1:55-69. doi:10.1017/s1041610292001157
22. Huntley JD, Howard RJ. Working memory in early Alzheimer's disease: a neuropsychological review. Int J Geriatr Psychiatry. 2010;25(2):121-132. doi:10.1002/gps.2314
23. Martínez-Nicolás I, Carro J, Llorente TE, García Meilán JJ. The Deterioration of Semantic Networks in Alzheimer's Disease. In: Wisniewski T, ed. Alzheimer's Disease. Codon Publications; 2019. Accessed February 19, 2021. http://www.ncbi.nlm.nih.gov/books/NBK552151/
24. Norton DJ, Parra MA, Sperling RA, et al. Visual short-term memory relates to tau and amyloid burdens in preclinical autosomal dominant Alzheimer's disease. Alzheimer's Research & Therapy. 2020;12(1):99. doi:10.1186/s13195-020-00660-z
25. Parra MA, Abrahams S, Logie RH, Méndez LG, Lopera F, Della Sala S. Visual short-term memory binding deficits in familial Alzheimer's disease. Brain. 2010;133(9):2702-2713. doi:10.1093/brain/awq148
26. Perrin A, Turner E. Smartphones help blacks, Hispanics bridge some – but not all – digital gaps with whites. Pew Research Center. Published August 20, 2019. Accessed March 15, 2021. https://www.pewresearch.org/fact-tank/2019/08/20/smartphones-help-blacks-hispanics-bridge-some-but-not-all-digital-gaps-with-whites/
27. Denervaud S, Christensen AP, Kenett YN, Beaty RE. Education shapes the structure of semantic memory and impacts creative thinking. npj Sci Learn. 2021;6(1):1-7. doi:10.1038/s41539-021-00113-8
28. Wechsler D. Wechsler adult intelligence scale–Fourth Edition (WAIS–IV). San Antonio, TX: NCS Pearson. 2008;22(498):1.
29. Lezak MD, Howieson DB, Loring DW, Fischer JS. Neuropsychological

Assessment. Oxford University Press, USA; 2004.
30. Quiroz YT, Sperling RA, Norton DJ, et al. Association Between Amyloid and Tau Accumulation in Young Adults With Autosomal Dominant Alzheimer Disease. JAMA Neurol. 2018;75(5):548-556. doi:10.1001/jamaneurol.2017.4907
31. Quiroz YT, Zetterberg H, Reiman EM, et al. Plasma neurofilament light chain in the presenilin 1 E280A autosomal dominant Alzheimer's disease kindred: a cross-sectional and longitudinal cohort study. The Lancet Neurology. 2020;19(6):513-521. doi:10.1016/S1474-4422(20)30137-X

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