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The Brain Health Assessment for Detecting and Diagnosing Neurocognitive Disorders

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Abstract

Background/Objectives—Brief cognitive screens lack the sensitivity to detect mild cognitive impairment (MCI) or support differential diagnosis. The objective of this study was to validate the 10-minute, tablet-based UCSF Brain Health Assessment (BHA) to overcome these limitations.

Design—Cross-sectional.

Setting—The University of California San Francisco Memory and Aging Center.

Participants—Older adults (N=347) including neurologically healthy controls (N=185), and individuals diagnosed with MCI (N=99), dementia (N=42), or as normal with concerns (N=21).

Measurements—The BHA includes subtests of memory, executive functions and speed, visuospatial skills, and language, and an optional informant survey. Participants completed the Montreal Cognitive Assessment (MoCA) and gold-standard neuropsychological tests. Standardized structural 3T brain MRI was performed on 145 participants.

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Conflicts of Interest

The remaining authors declare that they have no conflicts to disclose.

Author Contributions

KLP: study concept and design, analysis and interpretation of data, and preparation of manuscript.
TM: study concept and design, acquisition of subjects and data, analysis and interpretation of data, and preparation of manuscript.
SJE: study concept and design, acquisition of subjects and data, analysis and interpretation of data, and preparation of manuscript.
KR: study concept and design, and preparation of manuscript.
ETJ: study concept and design and acquisition of subjects and data.
NZRS: study concept and design and acquisition of subjects and data.
JJH: study concept and design and preparation of manuscript.
JS: acquisition of subjects and data and preparation of manuscript.
AGA: study concept and design, analysis and interpretation of data, and preparation of manuscript.
STF: study concept and design, interpretation of data, and preparation of manuscript.
BLM: study concept and design, interpretation of data, and preparation of manuscript.
KPR: study concept and design, analysis and interpretation of data, and preparation of manuscript.

Results—At a fixed 85% specificity rate, the BHA had a 100% sensitivity to dementia and 84% to MCI; the MoCA's sensitivity was 75% and 25% respectively. When the MCI sample was divided by diagnostic criteria as "likely" or "unlikely" AD, the BHA's sensitivity was 83% and 88% respectively, whereas the MoCA's sensitivity was 58% and 24%. The BHA subtests demonstrated moderate to high correlations with the gold-standard tests from their respective cognitive domains. Memory test performance correlated with medial temporal lobe volumes, executive/speed with frontal, parietal and basal ganglia volumes, and visuospatial with right parietal volumes.

Conclusion—The BHA demonstrated excellent combined sensitivity and specificity to detect dementia and MCI, including MCI due to diverse etiologies. The subtests provide efficient and valid measures of neurocognition that are key for differential diagnosis.

Keywords

Mild cognitive impairment; cognitive screening; primary care

INTRODUCTION

The early and accurate diagnosis of neurocognitive disorders benefits patients and families and is recommended as part of high-quality health care (1). A diagnosis prompts an evaluation for reversible causes, guides the selection of appropriate symptomatic treatments, allows patients and families to access supportive interventions, and focuses plans for future care needs. The diagnostic process typically starts in primary care with a concern expressed by the patient, family member, or clinician, or a positive cognitive screen (2) and is completed either in primary care or by a specialist.

Unfortunately, cognitive impairment and dementia are not diagnosed in more than half of cases. One barrier is the precision of brief cognitive screens used in primary care settings; while usually adequate for detecting dementia, they often fail to detect mild cognitive impairment (MCI) with high specificity (3, 4). Most screens emphasize the detection of memory dysfunction, a hallmark of Alzheimer's disease (AD), but neglect other domains such as visuospatial or executive functions (5). However, an estimated 40-50% of dementias are caused by non-AD diseases, most commonly Lewy body disease, frontotemporal lobar degeneration, and vascular disease, which frequently present with non-memory symptoms (6-8). Even AD can present with dysfunction in visuospatial, executive, or language rather than memory (9). Cognitive screens typically rely on a single, global cut-off score to determine if a patient is impaired, which may fail to detect circumscribed, non-memory deficiencies. Furthermore, few provide a valid profile of spared and impaired cognitive domains that could be used to assist with differential diagnosis. Also, brief screens rarely include informant surveys to evaluate functional decline and neurobehavioral changes. An ideal brain health assessment for primary care would efficiently detect all types of early decline, would simultaneously provide valid scores for key cognitive domains and level of functional impairment, and could be used by providers, along with other clinical information, to evaluate if a patient meets diagnostic criteria for common neurocognitive syndromes.

To address this need, we developed the UCSF Brain Health Assessment (BHA). Subtests were designed to efficiently evaluate four key cognitive domains that can be affected in neurocognitive disorders and that are recommended to be assessed by diagnostic criteria. Performance is summarized across domains, but the most affected domain also separately contributes to the determination of impairment, so that patients with a significant but circumscribed impairment are not missed. An informant survey elicits key symptoms for diagnosis, including socioemotional changes and level of functional impairment. The BHA features a 10-minute administration time and automated scoring and provider feedback, making it feasible to integrate into busy primary care and specialty practices.

The objectives of this study were to: 1) evaluate the BHA's accuracy in detecting mild cognitive impairment (MCI) and dementia, 2) evaluate the concurrent validity of the newly developed subtests of memory, executive/speed, and visuospatial skills with well-established neuropsychological tests from these domains, and 3) evaluate the neuroanatomical validity of these subtests using voxel-based morphometry. We intentionally evaluated MCI and dementia patients who were diverse in terms of the underlying disease predicted by consensus conference. This permitted sensitivity and specificity analyses separately for MCI likely and unlikely due to AD (objective 1) and maximized sample-wide variability in brain atrophy and behavior for the validity analyses (objectives 2 and 3) (10).

METHODS

Participants

This study was approved by the University of California, San Francisco (UCSF) Committee on Human Research. All participants provided written informed consent. A total of 347 participants including healthy older controls (N=185) and individuals diagnosed with MCI (N=99) (11), dementia (N=42) (i.e., major neurocognitive disorder) (12), or as normal with concerns (N=21) were recruited from longitudinal observational studies at the UCSF Memory and Aging Center. All participants including controls were diagnosed in multidisciplinary clinical consensus conferences, as detailed in Appendix S1.

Neuropsychological Assessment

The BHA is programmed in the TabCAT software platform, developed at UCSF (13). The BHA and the Montreal Cognitive Assessment (MoCA) (14) were administered to all participants. The MoCA was selected as a gold-standard comparison because it is a widely-used screening test of similar length that has been shown to be more accurate than other widely-used screening tests for the detection of MCI (15). The BHA included four subtests. The three new subtests, Favorites (memory), Match (executive function and speed), and Line Orientation (visuospatial), are described with screenshots in Figure 1 and in detail in Appendix S1. Animal Fluency (language), a widely-used test, was also administered; subjects named different animals as quickly as they could for 1 minute.

The BHA also includes the Brain Health Survey (BHS), which was self-administered by an informant who knew the participant well. On each question, the informant was asked to evaluate change in the participant's functional level or emergence of new neurocognitive

symptoms over the past 5 years. Twelve questions, from the ECog-12, were previously validated for the detection of MCI and dementia in a predominantly AD sample (16). To enhance the detection of less typical presentations, nine additional yes/no questions were added to the BHS (Appendix S2) to inquire about early neurocognitive or neurobehavioral symptoms typical of a non-AD disorder or an atypical presentation of AD.

Statistical Analyses

Sensitivity and specificity to dementia and MCI—Scores on the four subtests were converted to age-corrected z-scores, as described in Appendix S1. Each participant's mean z-score and lowest z-score were included in the discriminant function analyses to emphasize detection of both generalized cognitive impairment and domain-specific cognitive impairment when predicting diagnosis. Recognizing that an informant is not always available in primary care settings, the discriminant function analyses were calculated with and without the informant surveys included. We discriminated a group of 137 controls from a group comprised of participants diagnosed with dementia (N=30) or MCI (N=72). Next, this MCI sample was divided into whether participants met diagnostic criteria for the categories "likely due to AD" (N=29) or "unlikely due to AD" (N=43) as determined by the clinical consensus conference on the basis of their clinical and cognitive syndrome and structural MRI (9). Sample details (N=239) are provided in Supplementary Table S1. Receiver operating characteristic (ROC) curves were calculated for the discriminant scores for the BHA and the MoCA total. To minimize false positives, we emphasize a sensitivity level of 85% that is higher than that reported in many similar studies (3, 4), but also depict sensitivity values at alternate levels of specificity.

Concurrent validity analyses—Pearson correlations were computed for the three novel tests Favorites, Match, and Line Orientation with scores on widely-used measures of verbal memory (California Verbal Learning Test - 2nd Edition Long Delay Free Recall ("CVLT-II Standard" or the short form "CVLT-II Short") (17), visual memory (the Benson Complex Figure Recall) (18), executive functions and speed (Wechsler Adult Intelligence Test - 3rd Edition Digit Symbol) (19), and visuospatial skills (Benton Judgment of Line Orientation) (20). We hypothesized that the new tests would correlate highest with tests from the same domains. Sample details (N=136) are provided in Supplementary Table S2.

Neuroanatomical validity analyses—Participants underwent structural MRI scanning at the UCSF Neuroscience Imaging Center on a Siemens 3 Tesla TIM Trio scanner. We used voxel-based morphometry to determine the regional brain volumes that correlated with performance on Favorites, Match, and Line Orientation, controlling for age, sex, and total intracranial volume (Appendix S1). Based on established brain-behavior correlates of the domains each subtest was designed to measure, we hypothesized that the Favorites test would show anatomic correlation predominantly with brain regions mediating memory functions (i.e., bilateral hippocampus), the Match test would correlate predominantly with brain regions mediating information processing speed (i.e., basal ganglia) and executive functions (i.e., dorsolateral prefrontal and parietal cortex), and the Line Orientation test would correlate predominantly with brain regions involved in dorsal-stream visuospatial

processing (i.e., right parietal cortex). Sample details (N=145) are provided in Supplementary Table S3.

RESULTS

Sensitivity and Specificity Results

For dementia, the complete BHA (i.e., including the 4 subtests and the BHS that is comprised of the ECog-12 and the additional 9 questions) had an AUC of >.99. The AUC for the BHA cognitive tests without the BHS was nearly as high at .95, and the AUC for the MoCA was also good (.92). For MCI, the complete BHA had an AUC of .94. The BHA cognitive tests had an AUC of .83. Adding the ECog-12 increased the AUC to .89, and the additional 9 questions increased it further to .94. The MoCA had an AUC of .74. All AUC and sensitivity and specificity results to detect dementia and MCI, as well as after separating the MCI group into “likely” and “unlikely” due to AD, are provided in Figure 2.

Concurrent Validity Results

Each of the three novel BHA subtests showed their highest correlation with the neuropsychological test from the same domain (Supplementary Table S4). Favorites correlated with both verbal (CVLT-II Standard, r = .48; CVLT-II Short, r=.77) and visual (Benson Delay, r = .54) memory. Match correlated with executive function and speed (Digit Symbol, r = .83). Line Orientation correlated with visuospatial skills (Judgment of Line Orientation, r = −.46). All ps < .01.

Neuroanatomical Validity Results

As predicted, high scores on the Favorites memory test correlated positively with gray matter volumes in the bilateral temporal, insular, and frontal regions (Figure 3 and Supplementary Table S5). The largest and most significant regional correlates were in the bilateral medial temporal lobes and included the full extent of the right and left hippocampi, entorhinal cortices, and amygdalae. High scores on the Match executive function and speed test correlated positively with gray matter volumes predominantly in right and left lateral frontal, parietal, and subcortical regions (caudate, putamen, and thalamus). Low scores on the Line Orientation visuospatial test correlated positively with gray matter volumes in a cluster located in the right parietal lobe, specifically involving the right postcentral gyrus, the right supramarginal gyrus, and the right superior parietal lobule. All reported results were significant after family-wise error correction at $p^{FWE}<0.05$.

DISCUSSION

The efficient and accurate detection and diagnosis of early neurocognitive changes meets a significant need in primary care settings. This study found that the BHA provided 84% sensitivity to detect MCI and 100% to detect dementia at 85% specificity, and that the new BHA subtests produce valid cognitive domain subscores. While both the BHA and the MoCA accurately detected dementia, the BHA detected MCI more accurately. This finding was most evident in cases where the patient was diagnosed with MCI “unlikely due to AD”. In these patients, the BHA had a sensitivity of 88% while the MoCA had a sensitivity of

24% at 85% specificity. The three novel subtests of memory (Favorites), executive functions and speed (Match), and visuospatial skills (Line Orientation) were found to be valid measures of the cognitive constructs they were designed to measure. Each of these subtests exhibited moderate to high correlations with established tests from the same cognitive domains, and lower correlations with other domains. Also, each subtest correlated with regional brain volumes in predicted patterns: Favorites correlated with brain regions important for memory including the medial temporal lobes (21), Match correlated with brain regions important for executive functions and speed in the dorsal frontoparietal network and basal ganglia (22), and Line Orientation correlated with a cluster in the right parietal lobe (23). The remaining BHA cognitive subtest, Animal Fluency (widely used to assess the language domain), is sensitive to temporal and frontal lobe pathologies (24).

Currently, fewer than half of individuals with positive cognitive screening test results in primary care undergo any further diagnostic assessments. Systems level barriers that likely contribute to this gap include unavailability of specialists (2). This barrier could be reduced by supporting primary care practitioners to perform the necessary testing and diagnostic evaluations for uncomplicated patients. This is particularly crucial in rural areas where the access to specialist services is often reduced (25). The BHA provides valid subscores of key domains of cognition and function that are important for MCI (11) and dementia (12) diagnosis, and that could improve the diagnostic capability in the primary care setting by satisfying the criteria for common neurocognitive syndromes including both typical and atypical Alzheimer's disease (9), Lewy body dementia (26), and frontotemporal dementia (27, 28).

The BHS informant survey, comprised of the ECog-12 and 9 additional questions, substantially increased the sensitivity to detect MCI beyond the cognitive subtests. Adding the ECog-12 increased sensitivity from 72% to 82% to detect MCI patients "likely due to AD", with specificity fixed at 85%. This finding is consistent with previous work showing that the full-length version of this measure, independent of neuropsychological test performance, aids in predicting who will develop MCI, dementia, and disability (29, 30). The additional 9 questions, designed to elicit symptoms of less typical presentations of AD and of non-AD disorders, increased the sensitivity minimally beyond the ECog-12 in this "likely due to AD" group (83%). However, among the MCI patients diagnosed as "unlikely due to AD", while the ECog-12 increased sensitivity from 54 to 70%, the additional 9 questions increased it further to 88%. The BHS increased the sensitivity to dementia minimally from 95% to >99%. In sum, the quick informant surveys improved MCI detection rates substantially, but were less important when a patient had progressed to dementia. The additional BHS questions enhanced the ability to identify less typical AD or non-AD presentations, and more work is needed to understand their added value in real-world primary care samples. Importantly, these surveys are self-administered by the informant on paper or an electronic tablet with a simple response format, which may be convenient for implementation in busy primary care practices.

Additional work is underway to ensure the BHA is ready for translation into real-world primary care settings. The study sample was English speaking with moderate to high levels of education. Careful attention was paid during the BHA development to choose stimuli that

are culturally fair, including ethnically-diverse face stimuli, to reduce cultural bias. Broad utility cannot be assumed, however, and we are evaluating the validity of the translated and culturally adapted versions of the BHA in lower educated and culturally diverse populations. In primary care implementation studies, we plan to evaluate the BHA's utility among their MCI patients, who will on average be older, with more medical comorbidities, and a lower proportion of atypical causes of dementia. The BHA cannot be self-administered; some interaction with a clinical staff person and a quiet space are required, which may be an obstacle for some practices. The BHA's brevity, automated scoring, sensitivity, specificity, and the minimal training requirements for clinical staff are attributes that may contribute to its adoption in the primary care setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Joseph J. Higgins, MD is an employee of Quest Diagnostics and holds stock and stock options in the company. Bruce L. Miller, MD serves as Medical Director for the John Douglas French Foundation; Scientific Director for the Tau Consortium; Director/Medical Advisory Board of the Larry L. Hillblom Foundation; Scientific Advisory Board Member for the National Institute for Health Research Cambridge Biomedical Research Centre and its subunit, the Biomedical Research Unit in Dementia (UK); and Board Member for the American Brain Foundation (ABF). Katherine L. Possin PhD has received grant support from Quest Diagnostics and serves on the Alzheimer's Association Medical and Scientific Advisory Council - Northern California and Nevada Chapter. Katherine P. Rankin PhD has received grant support from Quest Diagnostics and the Rainwater Charitable Foundation.

Sponsors' Roles

All decisions regarding the study were made by the UCSF investigator team. Joseph Higgins, MD of Quest Diagnostics advised on study design and manuscript revisions. No other sponsors contributed to the design, methods, subject recruitment, data collections, analysis or preparation of the paper.

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Impact statement

We certify that this work is novel. The potential impact of this research on clinical care or health policy includes the following: The Brain Health Assessment could increase detection rates of mild cognitive impairment and dementia in everyday clinical settings.

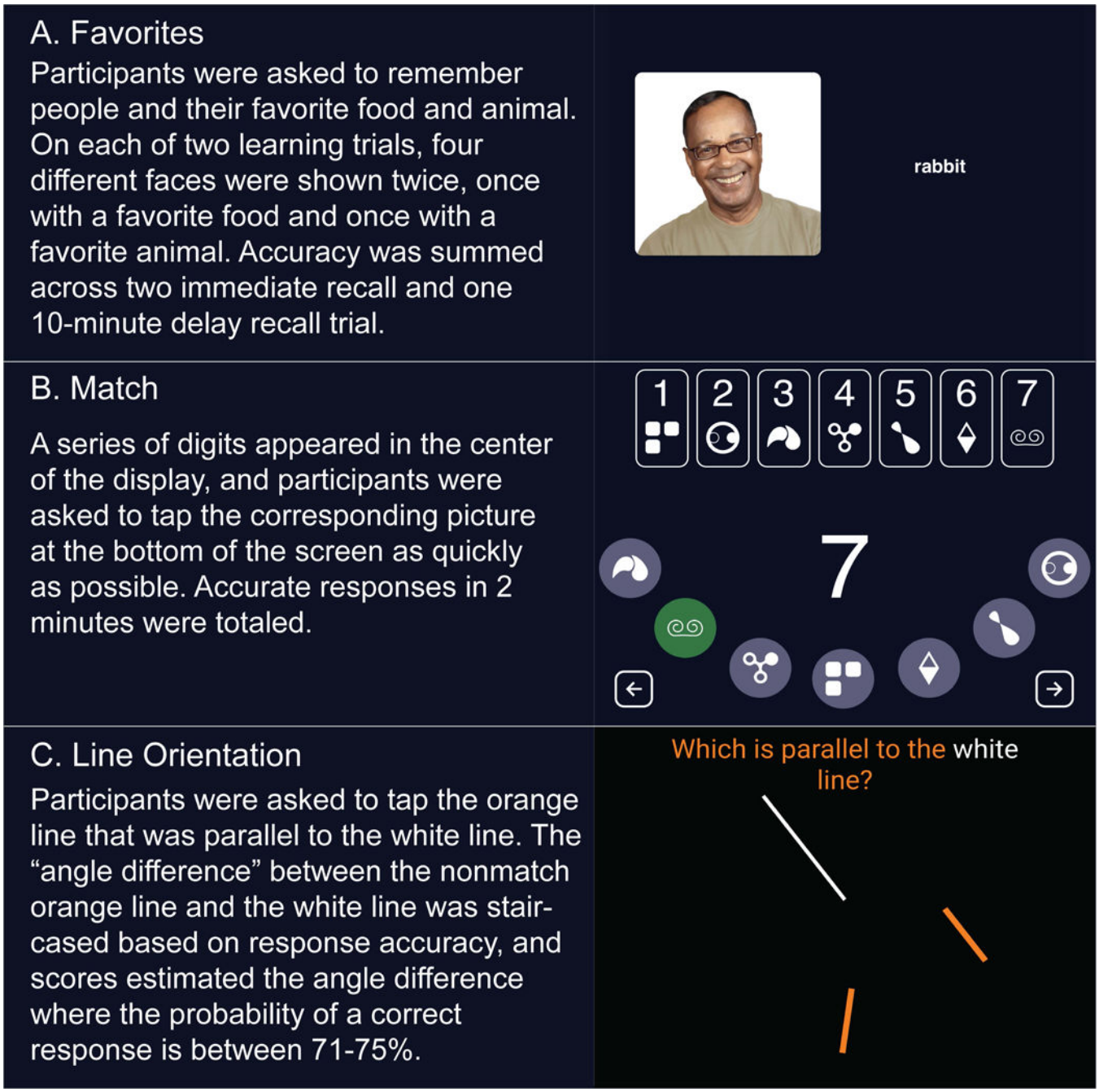
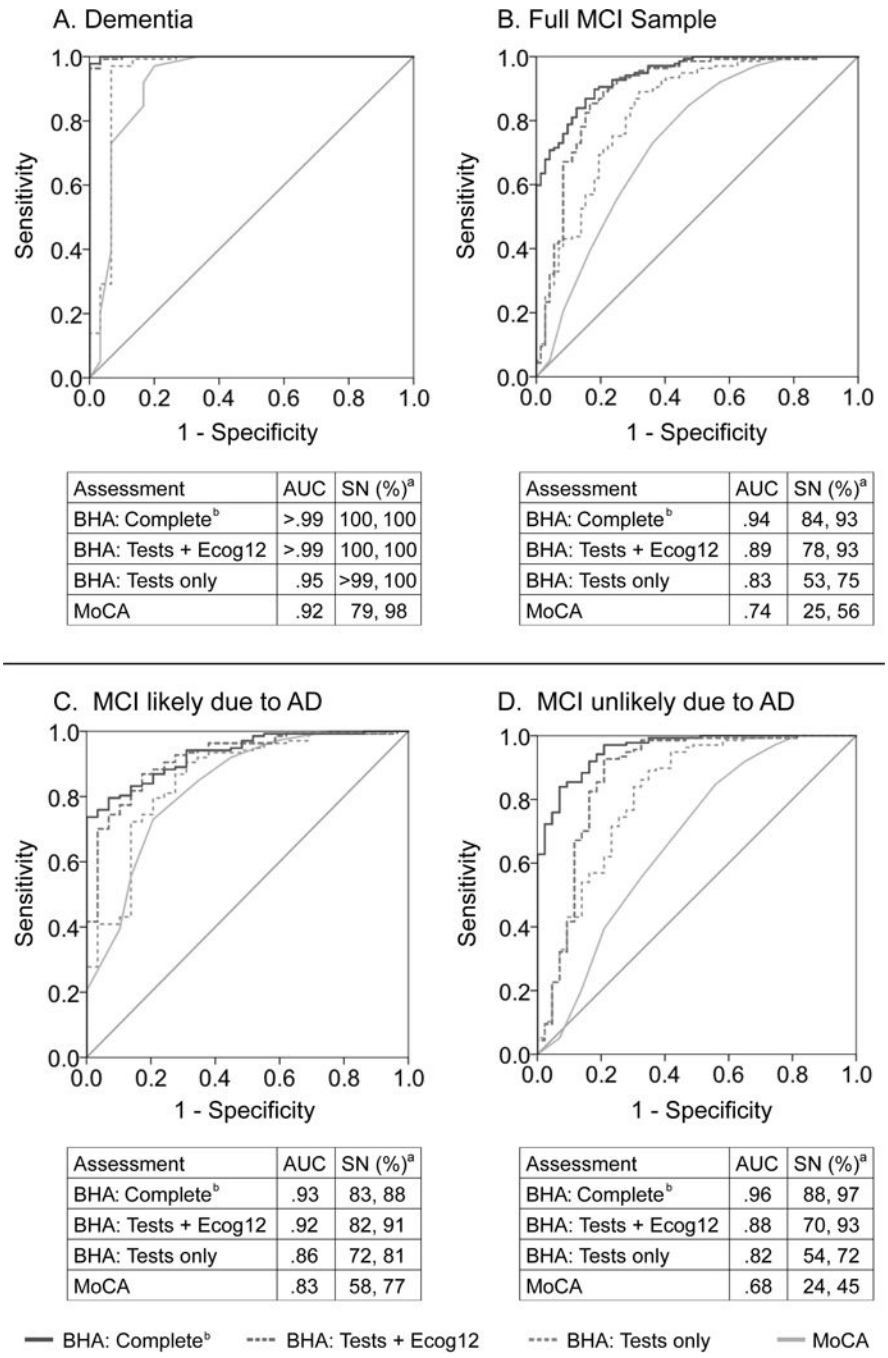


Figure 1.
BHA subtest descriptions and sample screenshots from A. Favorites, B. Match, and C. Line Orientation



Assessment	AUC	SN (%)[a]
BHA: Complete[b]	>.99	100, 100
BHA: Tests + Ecog12	>.99	100, 100
BHA: Tests only	.95	>99, 100
MoCA	.92	79, 98

Assessment	AUC	SN (%)[a]
BHA: Complete[b]	.94	84, 93
BHA: Tests + Ecog12	.89	78, 93
BHA: Tests only	.83	53, 75
MoCA	.74	25, 56

Assessment	AUC	SN (%)[a]
BHA: Complete[b]	.93	83, 88
BHA: Tests + Ecog12	.92	82, 91
BHA: Tests only	.86	72, 81
MoCA	.83	58, 77

Assessment	AUC	SN (%)[a]
BHA: Complete[b]	.96	88, 97
BHA: Tests + Ecog12	.88	70, 93
BHA: Tests only	.82	54, 72
MoCA	.68	24, 45

Figure 2.

Receiver Operating Characteristic Curves of the Brain Health Assessment and the Montreal Cognitive Assessment in separating patients diagnosed with dementia or mild cognitive impairment from neurologically healthy controls

[a]Sensitivity is provided at two levels of specificity: 85%, 75%.

[b]BHA: Complete was comprised of the subtests (operationalized by mean and lowest age-corrected z-score) and the BHS informant survey (the ECog-12 and the additional 9 questions).

Abbreviations: Sensitivity (SN), mild cognitive impairment (MCI), Brain Health Assessment (BHA), Montreal Cognitive Assessment (MoCA)

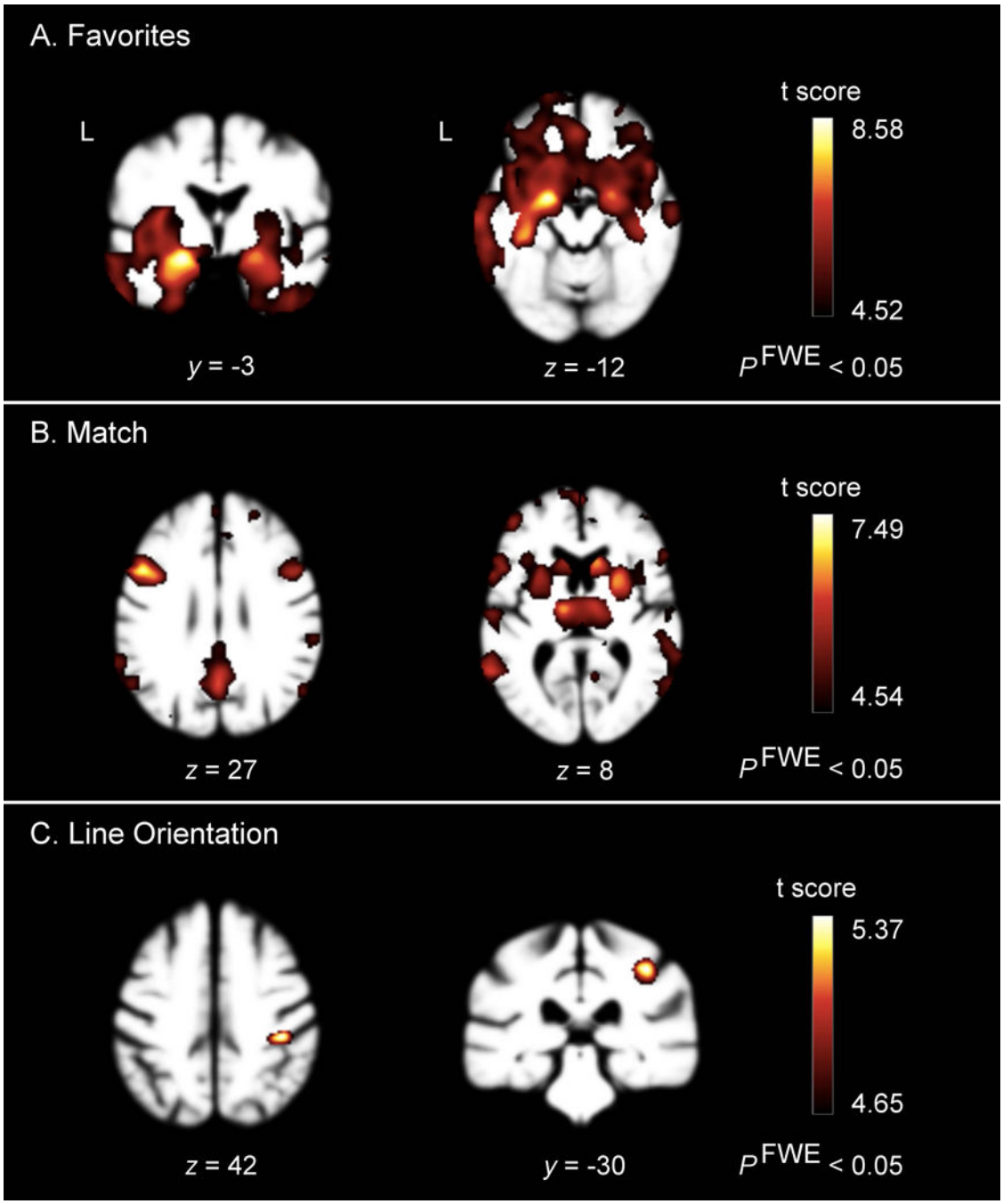


Figure 3.

Regional gray matter volume correlates of performance on the Brain Health Assessment Favorites, Match, and Lines subtests

FWE-corrected t-maps depicting regional brain volumes that correlated with (A) Favorites, (B) Match, and (C) Line Orientation performance, controlling for age, sex, and total intracranial volume (N = 145). In (A), scores on the Favorites subtest correlated positively with gray matter volumes in bilateral temporal regions. In (B), scores on the Match subtest correlated positively with gray matter volumes in bilateral frontal-subcortical regions. In (C),

scores on the Line Orientation subtest correlated with gray matter volumes in right parietal regions. Results are overlaid on a DARTEL-derived template. X, Y, and Z coordinates in the MNI space for each section are shown below the image. “L” denotes the left-right orientation of the images. All results depicted were significant at a corrected level ($p^{FWE}<0.05$).