Evaluating the Accuracy of Online and In-Clinic Subjective Cognitive Decline Assessments in Detecting Cognitive Impairment

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Table of Contents

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Abstract

Background: Scalable tools to efficiently identify individuals likely to have cognitive impairment (CI) are critical in the Alzheimer's disease and related dementias field. The Everyday Cognition scale (ECog) and its short form (ECog12) assess subjective cognitive and functional changes and are useful in predicting CI.

Objective: This study aimed to compare the ability of the online ECog and the in-clinic ECog in distinguishing between CI and cognitively unimpaired (CU) individuals, and to evaluate the effectiveness of the ECog12 compared to the full ECog in an online setting.

Methods: Participants were recruited from the Brain Health Registry (BHR; online) and Alzheimer's Disease Neuroimaging Initiative (ADNI; in-clinic) with available clinical diagnoses. Ability of ECog and ECog12 (Self- and study partner [SP]-ECog) to discriminate CI from CU were calculated using Receiver Operating Characteristic (ROC) curves. Area under the ROC curves (AUCs) between BHR and ADNI were compared using the DeLong test, as were AUCs between ECog12 and ECog in BHR.

Results: Both online and in-clinic ECog effectively discriminated CI from CU, with no significant differences in AUCs (BHR Self-ECog AUC = 0.722 vs. ADNI Self-ECog AUC = 0.769, DeLong P = .06; BHR SP-ECog AUC = 0.818 vs. ADNI SP-ECog AUC = 0.840, DeLong P = .50). Comparison between online ECog and ECog12 showed no significant differences in AUCs (Self-ECog AUC = 0.722 vs. Self-ECog12 AUC = 0.709, DeLong P = .18).

Conclusions: Online ECog, including the short-form ECog12, is as valid as in-clinic ECog for identifying clinically diagnosed CI, offering a cost-effective and accessible screening tool for large-scale online studies for identifying potential candidates for disease-modifying therapy.

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*Data used in preparation for this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI

investigators can be found at:

http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Short title: Online ECog and ECOg12 predicts MCI

Abstract

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Conclusions Online ECog, including the short-form ECog12, is as valid as in-clinic ECog for identifying clinically diagnosed CI, offering a cost-effective and accessible screening tool for large-scale online studies for identifying potential candidates for disease-modifying therapy.

Keywords: Subjective cognitive decline, Everyday Cognition scale, ECog-12, online, MCI, dementia

1 Introduction

Dementia is a syndrome characterized by cognitive and non-cognitive symptoms, affecting activities of daily living. Alzheimer's disease (AD) is the most common cause of dementia, marked by amyloid beta and tau neuropathology, which leads to memory decline and other cognitive symptoms that precede dementia (1). The recent development of disease-modifying medications such as aducanumab, lecanemab, and donanemab has brought new therapeutic options into clinical practice (2). Consequently, identifying individuals likely to have mild cognitive impairment (MCI)—potential candidates for disease-modifying therapy—has become increasingly important.

Neuropsychological tests are widely used as diagnostic tools for cognitive impairment (CI), differentiating between cognitively unimpaired (CU) individuals, those with MCI, and those with dementia (3). However, these tests are time-consuming, require trained professionals, and may not effectively capture fluctuations or progressive changes in cognitive function (4). The Everyday Cognition scale (ECog), developed by Farias et al., offers a practical, time-efficient alternative that can be self-administered, focusing on realistic assessments of daily functioning (5). A key feature of the ECog is its ability to assess subjective cognitive changes compared to 10 years ago, accounting for individual differences in baseline cognitive function. Additionally, it can address anosognosia—a common issue in individuals with MCI—through informant-administered ECog, which correlates more closely with clinical diagnoses than self-administered ECog (5-7). Past studies have demonstrated the utility of ECog in identifying diagnosis of MCI and predicting future conversion to MCI or dementia in healthy older adults (6-9).

The development of online platforms for clinical studies (10, 11) presents significant advantages for identifying individuals at risk of cognitive decline, including the ability to reach large populations and the cost- and time-effectiveness of reducing in-person visits. These platforms also facilitate longitudinal data collection and the monitoring of participants' cognitive health. The Brain Health Registry (BHR) has administered remote, unsupervised ECog to > 64,680 participants since

2014 (12). Recently, the Alzheimer's Disease Neuroimaging Initiative 4 (ADNI4) (13) began remote, unsupervised administration of the ECog12, a validated short form of ECog (7, 8), to participants and study partners in the ADNI Digital Study (13). Although ECog and ECog12, when administered in-person in the clinic, have proven effective in detecting CI, amyloid positivity, and predicting the progression to MCI or AD (5-7, 9, 14), the validity and utility of the online ECog or ECog12 have not been compared with their in-clinic pen-and-paper counterparts.

The overall goal of this study was to determine the ability of the online ECog to distinguish CI from CU individuals. We investigated three hypotheses: (1) the online ECog will be associated with clinically diagnosed CI; (2) the online ECog will show comparable association with CI as the in-clinic ECog; and (3) the online ECog12 will be as effective in identifying CI as the full-length online ECog. These hypotheses were tested by estimating associations between ECog and clinical diagnosis and comparing the accuracy of in-clinic versus online ECog and ECog12 versus the full ECog to distinguish diagnostic groups.

2. Methods and Materials

2.1 Participants

Participants in this study were recruited from two sources: the BHR Electronic Validation of Online Methods to Predict and Monitor Cognitive Decline (eVAL) study (15, 16) for the online component, and the ADNI study for the in-clinic component.

2.1.1 BHR eVAL

The BHR is an online neuroscience registry dedicated to the evaluation and monitoring of various cognitive disorders in a remote setting. Participants and their invited study partners (SPs) visit the BHR website to complete remote cognitive assessments every six months (7). The eVAL study is a multisite study that used the BHR platform to validate electronic versions of existing in-clinic cognitive monitoring instruments through the internet-based BHR platform. All eVAL participants were also evaluated in an in-clinic setting (17). Participants enrolled in eVAL from BHR at UCSF and the Alzheimer's Disease Research Centers at the University of Alabama at Birmingham, Mayo Clinic in Rochester, MN, and Washington University (17). This study was approved by the Institutional Review Board (IRB) of UCSF. Participants provided online informed consent upon enrollment and written informed consent at their first in-clinic visit for enrollment in the eVAL study.

2.1.2 ADNI

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). Launched in 2003 as a collaboration between public and private sectors under the leadershiP of Principal Investigator Dr. Michael W. Weiner, ADNI aims to determine if serial magnetic resonance imaging, positron emission tomography scans, other biological markers, along with clinical and neuropsychological evaluations can effectively track the progression of MCI and early AD. For the latest updates, visit www.adni-info.org. All study protocols were approved by the

IRB of each participating study center, and participants provided written informed consent.

2.1.3 Inclusion criteria

This study included participants from BHR eVAL and ADNI with following criteria: i) age between 55-90 years; ii) have completed Self-ECog or SP-ECog questionnaire, or both; iii) have a clinical diagnosis of CU or MCI; iv) underwent both ECog questionnaire and clinical diagnostic evaluation at the baseline evaluation period.

2.2 Measurement

2.2.1 Everyday Cognition Scale

This study utilized baseline ECog scores from all participants. ECog is a 39-item questionnaire that assesses subjective changes in cognition and instrumental activities of daily living compared to 10 years ago (5). Each item is rated on a 1-4 Likert scale (1, no change or better; 2, questionable or occasionally worse; 3, consistently a little worse; 4, consistently much worse), with the total score being the average of all responses and higher scores indicating greater decline. ECog ratings can be provided either by the individual themselves (self-reported ECog or Self-ECog) or by a study partner (study partner-reported ECog or SP-ECog). In this study, SP-ECog was used when available. ECog was assessed in an online unsupervised setting in BHR eVAL study and in in-clinic setting in ADNI study.

ECog12 is a short form of ECog that was developed using selected 12 items throughout all cognitive domains (8). As ECog12 has shown a reduced testing time with high consistency and clinical validity, and several studies have used the ECog12 (6, 8, 18). For this study, the full ECog was administered in both BHR and ADNI. We derived the ECog12 score from the full ECog by selecting the 12 items from the original, full-length instrument, and taking the average of the 12 items.

2.2.2 Clinical diagnosis

All participants in this study underwent clinical diagnostic evaluations. In the BHR eVAL study, participants were clinically diagnosed as CU, having MCI, or very mild dementia according to the Uniform Data Set version 3. This standard was developed by the National Alzheimer's Coordinating Center under the supervision of the National Institute on Aging and is implemented across all U.S. Alzheimer's Disease Centers (19).

In ADNI, participants were evaluated for an initial diagnosis using scores from the Clinical Dementia Rating scale (CDR), the Mini Mental State Exam, as well as clinical judgement. Participants were categorized into baseline diagnostic categories as follows: Cognitively Normal across all ADNI phases (1/GO/2/3), Subjective Memory Concern (SMC) in ADNI 2, Early MCI (EMCI) and Late MCI (LMCI) in ADNI GO/2, MCI in ADNI 1/3, and AD across all ADNI phases. For this study, Cognitively Normal, SMC, and MCI (EMCI, LMCI, and MCI) participants were included.

Clinical diagnoses in this study were categorized into two groups: CU, which includes CU from the BHR eVAL study and Cognitively Normal and SMC from ADNI; and CI, which includes MCI and very mild dementia from the BHR eVAL study and Early MCI, Late MCI, and MCI from ADNI study.

2.2.3 Demographic and clinical information

Participants' demographic and clinical information were included in this study: age at baseline, gender (male and female), years of education, race (African American, Asian, Caucasian, and Other [American Indian/Alaskan Native, Hawaiian/Other Pacific Islander, more than one, and unknown/declined to state race]).

Baseline CDR was obtained from both cohorts (20). We used the CDR sum of box score, which is a reliable and valid diagnostic and dementia staging measure (21), with higher scores

indicating a greater level of CI. Geriatric Depression Scale-Short Form (GDS) was also obtained for both studies (22). To account for the correlation between GDS and ECog in this study, one GDS item regarding memory symptoms (“Do you feel you have more problems with memory than most?”) was excluded from the GDS score, thus making the total score ranging from 0 to 14. A higher score indicates more depressive symptoms. Subjective memory concern was also obtained from both cohorts and was a yes-or-no question: "Are you concerned that you have a memory problem?" in BHR eVAL and “Are you concerned that you have a memory or other thinking problem?” in ADNI.

2.3 Statistical analysis

2.3.1 Descriptive analysis

We produced descriptive statistics according to the diagnostic groups (CU and CI) and online or in-clinic study setting (BHR and ADNI) and compared demographic and clinical information and ECog scores between groups using independent t-test and chi-squared test.

2.3.2 Ability of online ECog for predicting CI

To test the first hypothesis that the online ECog can distinguish diagnostic groups, we performed binomial logistic regression analyses with the diagnostic grouP (CU or CI) as the dependent variable. We then calculated the area under the curve (AUC) using Receiver Operating Characteristic curve. Subsequent metrics including optimal ECog cut point score, sensitivity, specificity, and Youden index were also calculated based on the predicted value of a logistic model with ECog score, age, gender, years of education, race, and GDS.

2.3.3 Comparison between online and in-clinic ECog

To compare the ability of online ECog for discriminating CI from CU to that of in-clinic ECog, we compared the AUC for discriminating CI from CU in BHR to the AUC in ADNI using the DeLong test.

2.3.4 Comparison between ECog12 and ECog in online setting

To compare the effectiveness of online ECog12 in distinguishing CI from CU to the full-length online ECog, we also compared the AUC of ECog12 and AUC of full-length ECog in BHR. Statistical significance was set at $P < .05$, there was no correction for multiple comparisons, and R version 4.3.2 (R Core Team, 2023) was used in all analyses.

3 Results

3.1 Participants

3.1.1 Demographic and clinical information

A total of 1,801 participants were included in this study (n = 428 in BHR; n = 1,373 in ADNI). Table 1 presents the demographic and clinical information of participants, including comparisons across diagnostic groups and between the BHR and ADNI cohorts. Differences between CU and CI were observed in gender (x^2= 6.01, P = .014), CDR sum of boxes (t = -7.37, P < .001), and subjective memory concern (t = 37.62, P < .001) in BHR. In ADNI, differences were found in all demographic and clinical variables except for age. BHR participants showed higher GDS scores in both CU (t = 14.51, P < .001) and CI (t = 5.80, P < .001) groups compared to ADNI.

3.1.2 ECog scores in both groups

Table 1 displays ECog scores. In all cases, Self-ECog scores tended to be higher than SP-ECog scores although not statistically proven. The only significant difference between ADNI and BHR was observed in Self-ECog scores within the CI grouP (ADNI > BHR; t = -2.21, P = .03).

3.2 Association between ECog scores and cognitive impairment

Table 2 presents the AUC values for distinguishing CI from CU in BHR and ADNI. The AUCs were moderate in BHR (0.709 – 0.818) and ADNI (0.747 – 0.840). After adjusting for age, gender, years of education, race, and GDS, the AUCs remained fair to moderate in both BHR and ADNI (0.724 – 0.851). Subsequent metrics including optimal cut point, sensitivity, specificity, and diagnostic accuracy are also presented in Table 2 for both studies.

3.3 Comparing AUCs between BHR and ADNI

Figure 1A and 1B illustrate the AUCs of BHR and ADNI and their comparisons. Both Self-ECog (BHR AUC = 0.722, ADNI AUC = 0.769, DeLong P = .16) and SP-ECog (BHR AUC = 0.818,

ADNI AUC = 0.840, DeLong *P* = .50) showed comparable AUC values between BHR and ADNI.

3.4 Comparing AUCs between ECog and ECog12 in BHR

Figure 1C and 1D depict the comparison between ECog and ECog12 in BHR. Self-ECog and Self-ECog12 demonstrated comparable AUCs (Self-ECog AUC = 0.722, Self-ECog12 AUC = 0.709, DeLong *P* = .18), while SP-ECog exhibited higher AUC than SP-ECog12 (SP-ECog AUC = 0.818, SP-ECog12 AUC = 0.777, DeLong *P* = .001)

4 Discussion

4.1 Principal Results

This study investigated the effectiveness of a measure of subjective cognitive decline, ECog, to detect CI in two cohorts: online in BHR and in-clinic in ADNI. The first finding was that the ECog demonstrated moderate accuracy in distinguishing CI and CU individuals in both BHR and ADNI. The second finding was that the online Self- and SP-ECog in BHR showed comparable ability to detect CI, similar to the in-clinic ECog scores in ADNI. The third finding was that the ECog12, the short form of the ECog, was as effective as the full-length ECog for detecting CI in the BHR. These results indicate that ECog scores, whether administered online or in-clinic, and in both short-form and full-length versions, are useful in identifying clinically diagnosed CI individuals.

The first finding of this study is that the online ECog demonstrated a moderate association with CI in an online cohort. Both online Self- and SP-ECog scores effectively differentiated between MCI and CU individuals. This result aligns with previous research that has shown a strong association between online SP-ECog and self-reported diagnoses of MCI or AD (7). Our results showed additional evidence that both online Self- and SP-ECog are effective in identifying individuals who are clinically diagnosed with CI. Previous in-clinic studies have reported that informant-reported ECog scores are better at predicting CI from CU than self-reported scores (6, 8, 9). A prior study focusing on older adults with CI found that online SP-ECog could distinguish AD dementia from MCI, while Self-ECog could not (23). The ability of both Self- and SP-ECog to identify CI in this study might be due to the fact that most participants in BHR had mild cognitive symptoms (24), which makes it less likely that they are unaware of their cognitive status (25). It is also noteworthy that establishing online ECog cut point scores with good sensitivities, specificities, and accuracies is useful as a screening tool to detect CI in the older adult population. Our findings demonstrate the utility of online ECog for detecting the clinical diagnosis of CI, particularly in mildly impaired populations.

The second finding is that online ECog and in-clinic ECog produced comparable results in discriminating CI from CU. Previous studies have found that online ECog scores closely correspond with in-clinic ECog scores (26). Our study newly revealed that online ECog is as effective as in-clinic ECog for detecting CI from CU. Although online scales offer advantages in convenience, cost-effectiveness, and reduced environmental impact, they also face challenges such as digital accessibility, response rates, and selection bias (27, 28). The trend towards overall higher discriminative AUC values, although not significant, in ADNI compared to BHR might be attributed to the nature of online scales, including response quality, lower engagement due to convenience, and potential technical issues (29). Despite these challenges, the similarity of the association between ECog and clinical diagnosis of MCI between online and in-clinic setting suggests that online ECog can be used as effectively as in-clinic ECog for CI screening.

The third finding is that Self-ECog12 performed comparably to full-length Self-ECog in distinguishing CI from CU in an online setting. ECog12, derived from the original 39-item ECog, maintains good psychometric properties for various cognitive domains, including memory, visuospatial function, language, and executive function (8). Previous studies have shown that ECog12 is as effective as full-length ECog in identifying the risk of MCI (6, 9). The fact that online ECog12 shows a similar association with the diagnosis of CI versus CU as the 39-item ECog supports its use in online clinical studies like BHR. Recent large-scale neuroscience studies have started collecting online data from questionnaires about cognitive function, leveraging extensive and longitudinal collections (30-32). ADNI4, the current phase of ADNI, also recently implemented online ECog12 in a novel online screening approach to aid in selecting participants for plasma AD biomarker analysis and in-clinic evaluation (13, 18). Although SP-ECog12 showed a significantly lower probability of detecting CI from CU compared to SP-ECog in this study, online ECog12 remains a useful and time-efficient tool for identifying individuals at risk of MCI in online settings.

Recently, advances in online technology have allowed the use of online cognitive tests to

identify CI with convenience and scalability (33, 34). Self-administered online digital neuropsychological tests are an effective method for identifying CI, offering benefits such as accessibility, efficiency, and diagnostic accuracy for dementia (35). Many well-known in-clinic tests, including the Montreal Cognitive Assessment, Cogstate Brief Battery, and Cambridge Neuropsychological Test Automated Battery (CANTAB®), have been adapted for online use (36-39). Although neuropsychological tests objectively measure cognitive abilities through rigorous standardized tasks, ECog, which is a subjective cognitive decline measure, captures the individual's or their informant's perception of cognitive and functional changes in real-life, which can provide early indicators of cognitive decline that objective tests might miss (5, 25). As ECog and ECog12 can be easily administered online with validity for identifying CI from CU, integrating both objective and subjective measure of cognitive decline in online studies could enhance early detection of MCI who are potential candidates for disease-modifying therapy and comprehensive understanding of cognitive health.

4.2 Limitations

This study has several limitations. Firstly, the BHR eVAL study and ADNI consists predominantly of participants with higher education, most of whom are non-Latinx white. This lack of demographic diversity is likely to limit the generalizability of the results. The second limitation is that this study was not originally designed to compare online and in-clinic populations. Instead, it compared these populations retrospectively, meaning that the recruitment process was not perfectly controlled from the outset and there may be participation self-selection biases. Thirdly, the cross-sectional design of this study limits the interpretation of the results due to the lack of longitudinal cause-and-effect relationships between ECog scores and clinical diagnoses.

4.3 Conclusions

Subjective cognitive changes measured in a remote, unsupervised, online setting distinguished CI

from CU diagnostic groups with moderate accuracy. Compared to in-clinic scales, the online ECog showed comparable ability to discriminate CI from CU. ECog12, a shorter form developed to increase brevity, also demonstrated a moderate association with clinical diagnosis in an online setting. These results highlight the value of the online ECog as a valid tool for identifying older adults with MCI in an online clinical study. In summary, the online ECog, including its short form, can serve as an effective screening tool to identify and monitor individuals with MCI. Moreover, it offers a time- and cost-efficient method for referring at-risk individuals to thorough evaluation processes in online clinical studies.

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6 Conflict of interest

Manchumad Manjavong, Adam Diaz, Miriam T. Ashford, Anna Aaronson, Joseph Eichenbaum, R. Scott Mackin, Rachana Tank, Melanie J. Miller, Bernard Landavazo, Erika Cavallone, Diana Truran, Monica R. Camacho, Juliet Fockler, Derek Flenniken, and Sarah Tomaszewski Farias report nothing to disclose; Jae Myeong Kang reports grants from Gachon University, during the conduct of the study; Rachel Nosheny reports grants from NIA, during the conduct of the study; Michael Weiner reports grants from National Institutes of Health (NIH)/NINDS/National Institute on Aging, grants from Department of Defense (DOD), grants from California Department of Public Health (CDPH), grants from University of Michigan, grants from Siemens, grants from Biogen, grants from Hillblom Foundation, grants from Alzheimer's Association, grants from Johnson & Johnson, grants from Kevin and Connie Shanahan, grants from GE, grants from VUmc, grants from Australian Catholic University, grants from The Stroke Foundation, grants from Veterans Administration, personal fees from Boxer Capital, personal fees from Cerecin, personal fees from Clario, personal fees from Dementia Society of Japan, personal fees from Eisai, personal fees from Guidepoint, personal fees from Health and Wellness Partners, personal fees from Indiana University, personal fees from LCN Consulting, personal fees from Merck SharP & Dohme Corp., personal fees from NC Registry for Brain Health, personal fees from Prova Education, personal fees from T3D Therapeutics, personal fees from University of Southern California (USC), personal fees from WebMD, personal fees from China Association for Alzheimer's Disease (CAAD) , personal fees from Taipei Medical University, personal fees from AD/PD Congress, personal fees from Cleveland Clinic, personal fees from CTAD Congress, personal fees from Foundation of Learning, personal fees from Health Society (Japan), personal fees from INSPIRE Project; U. Toulouse, personal fees from Japan Society for Dementia Research, personal fees from Korean Dementia Society, personal fees from National Center for Geriatrics and Gerontology (NCGG; Japan), personal fees from University of Southern California (USC)., other from Alzeca, other from Alzheon, other from ALZ Path, other from Anven, outside the

submitted work.

7 Abbreviations

AD, Alzheimer's disease; AUC, area under curve; ADNI, Alzheimer's Disease Neuroimaging Initiative; BHR, Brain Health Registry; CDR-SOB, Clinical Dementia Rating-Sum of Boxes; CI, cognitively impaired; CU, cognitively unimpaired; eCDR, Electronic Clinical Dementia Rating; ECog, Everyday Cognition Scale; ECog12, short version of ECog; eVAL, Electronic Validation of Online Methods to Predict and Monitor Cognitive Decline; EMCI, Early Mild Cognitive Impairment; GDS, Geriatric Depression Scale; IRB, Institutional Review Board; LMCI, Late Mild Cognitive Impairment; MCI, Mild Cognitive Impairment; Self-ECog, self-reported ECog; SP-ECog, study partner-reported ECog; ROC, Receiver Operating Characteristic; SMC, Subjective Memory Concern

8 Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Supplementary Files

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Figures

Receiver operating curves for predicting cognitive impairment. AUC, area under curve; BHR, Brain Health Registry; ADNI, Alzheimer's Disease Neuroimaging Initiative; ECog, Everyday Cognition Scale; Self-ECog, self-reported ECog; SP-ECog, study partner-reported ECog; ECog12, short version of ECog.