HHS Public Access
Author manuscript
J Am Geriatr Soc. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:
J Am Geriatr Soc. 2017 June ; 65(6): 1152–1158. doi:10.1111/jgs.14835.

Early functional limitations in cognitively normal older adults predicts diagnostic conversion to mild cognitive impairment

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Abstract

Background and Objectives—There is increasing evidence that changes in everyday functional abilities are among the first signs of incipient neurodegenerative disease. The present study sought to examine whether specific types of early functional limitations in cognitively normal older adults are associated with the subsequent development of mild cognitive impairment (MCI), as well as the relative predictive value of self- versus informant-report in predicting diagnostic conversion to MCI.

Design—Participants received baseline and annual multidisciplinary clinical evaluations including a physical and neurological exam, imaging, lab work, and neuropsychological testing.

Setting—Data used in this study was collected as part of a longitudinal research cohort at the University of California, Davis Alzheimer's Disease Center (ADC).

Participants—Participants (n = 324) were diagnosed as having normal cognition at study baseline, had an informant who could complete informant-based ratings, and had at least one follow-up visit.

Measurements—Participants and informants each completed The Everyday Cognition (ECog) scale, an instrument designed to measure everyday function across six cognitive domains.

Results—Both self- and informant-reported functional limitations on the ECog were associated with a significant increase in risk of diagnostic conversion to MCI (informant: HR = 2.0, 95% CI =

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Conflict of Interest
No potential conflict of interest was reported by the authors.

Author Contributions
All authors have contributed substantially to the study (Sarah Tomaszewski Farias, Karen Lau, Katherine Denny, Cheyanne Barba, and Anthony Mefford were involved in interpretation and manuscript preparation, and Danielle Harvey was involved in data interpretation and manuscript preparation).

1.3–3.2, $p = .002$), with self-report having a slightly higher hazard ratio (HR = 2.3, 95% CI = 1.4–3.6, $p < .001$). When controlling for baseline cognitive abilities, the effect remained significant for both self- and informant-reported functional limitations.

Conclusion—Deficits in everyday memory and executive function domains were the strongest predictors of diagnostic conversion to MCI. These results indicate detection of early functional limitations may be clinically useful in assessing the future risk of developing cognitive impairment in cognitively normal older adults.

Keywords

functional ability; normal cognition; mild cognitive impairment; self-report; informant report

Introduction

Loss of autonomy is a top concern of older adults.[1] A hallmark feature of a dementia syndrome is functional disability, or loss of independence in performing major instrumental activities of daily living (IADL) critical for autonomous living (i.e., managing finances.). While loss of independence in major IADLs represent important disease milestones, the more subtle functional limitations that predate disability develop gradually and early in the disease process.[2,3] A better understanding of when functional changes start to emerge and what types of early functional limitations are associated with risk of progressive disease and loss of independence is critical to implementing early detection strategies and informing when and how to intervene.

Mild cognitive impairment (MCI) is a transitional state between normal cognition (NC) and dementia. Subtle changes in everyday functional abilities are evident in MCI[4–10] and a greater degree of functional limitations are associated with a faster rate of cognitive decline[11,12] and disease progression/conversion to dementia.[13–20] Subtle functional changes may be detectable among NC older adults who eventually develop MCI/dementia. Population based studies have shown subtle functional changes can predate a dementia diagnosis by 10–12 years.[2,3] Similarly, a longitudinal study of functional trajectories demonstrated that NC older adults who later develop MCI/dementia evidenced greater everyday functional limitations at baseline, and faster functional decline over time compared to cognitively stable older adults.[21]

Little is known about which types of functional limitations develop earliest and are associated with a particularly poor prognosis. Among those with MCI, functional tasks most dependent on higher-level cognitive abilities are affected earliest.[19,22] Among non-demented older adults, functional limitations related to everyday memory and executive abilities have been shown most strongly associated with risk of incident IADL dependency and conversion to dementia.[18]

Questionnaire-based measures, completed by either the older individual, or knowledgeable informant are used to measure the magnitude of change in functional abilities from an individual’s baseline. When assessing older adults with dementia, self-report is often inaccurate due to poor insight. However, informant-reported functional changes has been shown to discriminate between individuals with or without dementia,[23–26] to be related to objective neuropsychological performance[16] and to disease markers (e.g., brain atrophy).[16,27] Among individuals with MCI, evidence for the validity of self-reported functional changes is mixed.[28–31] Debate exists as to whether self- or informant-report rated declines in everyday function is most useful in those with minimal cognitive impairment.[10,32–35] Self-reported functional decline among NC older adults has been associated with risk of preclinical Alzheimer's.[36,37]

Taken together, it appears that functional changes progress over an extended period of time and are an early indicator of neurodegenerative disease. It remains unclear when the earliest changes can be detected, what types of functional changes occur first, and how best to detect such early changes. Thus, goals of this study are: 1) to evaluate whether early functional limitations among NC older adults are associated with increased risk of developing MCI, 2) determine whether there are particular types of functional limitations associated with increased risk of MCI, and 3) evaluate the relative predictive value of self- versus informant-reported functional abilities in predicting conversion to MCI. We hypothesized that NC older adults with greater functional limitations at study baseline would evidence higher risk of subsequent diagnostic conversion to MCI. Based on the contribution of executive function and memory abilities on everyday function,[16,29,38] we hypothesize that functional limitations related to *everyday* executive and memory abilities would pose the greatest risk for a future conversion to MCI. We hypothesized that both self- and informant-report would predict development of MCI. Because subtle decrements in cognition may aid in identifying those at greater risk for the development of MCI,[39,40] prediction models included baseline measures of neuropsychological function.

Methods

Participants

Data used in this study was collected as part of a longitudinal research cohort at the University of California, Davis Alzheimer's Disease Center (ADC). Participants were recruited through clinic referrals and community outreach. Participants: 1) spoke English or Spanish (27 participants were tested in Spanish), 2) had an informant with whom the participant had regular contact and could complete informant-based ratings, 3) were diagnosed as having NC at study baseline, and 4) had at least one follow-up visit. Exclusion criteria included unstable major medical illness or current debilitating psychiatric disorder (milder forms of depression were acceptable).

All participants received baseline and annual diagnostic evaluations that included a physical and neurological exam, imaging, lab work, and neuropsychological testing from the Alzheimer's Disease Uniform Dataset Neuropsychological Battery.[41] Diagnoses at each annual visit were categorized by syndrome: NC or MCI according to standardized criteria.[42] Individuals with MCI could not have impairments in basic activities of daily livings (ADLs) or be dependent in IADLs. Clinical diagnoses were made without knowledge of the ECog (the primary functional assessment predictor).

A total of 324 older adults who were NC at study baseline and at least one follow-up assessment were included in the study (see Tables 1 and 2 for demographic data). On average, the sample was followed for 4 years. Average time from study baseline to development of MCI was one year shorter (3 years) than the average length of follow up for those who did not convert (on average non-converters were followed 4 years). Converters were slightly older. The MMSE, and neuropsychological performance was slightly lower in participants who progressed to MCI although scores were well within the average range consistent with their initial diagnosis of NC. As measured by both the informant- and self-rated ECog at study baseline, participants who progressed to MCI showed slightly worse function (higher Total ECog scores) as well as several of the domain scores (Everyday Memory, some everyday executive domains). All participants signed informed consent and human subject involvement was approved by appropriate institutional review boards.

Assessment of everyday functional limitations

The Everyday Cognition (ECog) scale is an informant- and self-rated questionnaire of cognitively-based everyday abilities. It was designed to be sensitive to mild functional limitations that predate loss of independence and are relevant to functional changes associated with MCI.[6,19] The ECog comprises of 39 items on which the participant's current level of everyday functioning is compared to 10 years earlier. Items are rated on a four-point scale: 1= better or no change; 4= consistently much worse. Higher scores indicate greater limitations. A total score was calculated by summing all of the ratings and dividing by the number of items completed. Confirmatory factor analysis supports the construct of everyday function as a multidimensional model with six distinct cognitively-based domains that correspond objectively with specific domains of neuropsychological function.[19] The domains include: Everyday Memory, Everyday Language, Everyday Visuospatial abilities, Everyday Planning, Everyday Organization, and Everyday Divided Attention. The ECog has good test-retest reliability ($r = .82$, $p < .001$).[19] Confirmatory factor analysis has supported the theoretically proposed structure of the instrument,[19] it has been shown to discriminate between diagnostic groups,[20] and to be related to objective measures of cognition and biomarkers of neurodegenerative disease.[9,43] Example ECog items are included in Table 3 and the full instrument is available at: http://dx.doi.org/10.1037/0894-4105.22.4.531.supp.

Neuropsychological assessment

Cognitive functioning was assessed using the Spanish English Bilingual Neuropsychological Assessment Scales battery (SENAS), which has undergone extensive development as a battery of cognitive tests relevant to diseases of aging.[44–46] This study used two composites: Episodic Memory (list-learning) and Executive Function (working memory).

Statistical analyses

Two-sample t-tests, Wilcoxon rank-sum tests (for ECog scores, follow-up time) and chi-square tests (for categorical variables) were used to compare those who progressed to MCI to those who remained stable on demographics, functional limitations and neuropsychological function. Cox proportional hazards models were used to assess associations between functional limitations and diagnostic conversion to MCI. Those who did not develop MCI were considered censored at the last assessment. Models were adjusted for baseline age, education, and ECog domain or total score (informant- or self-reported). Secondary analyses assessed the association between functional limitations and incident MCI independent of episodic memory and executive function. Sensitivity analyses removed participants who progressed to MCI, but later were reclassified as normal (n=7; 4 of the 7 were later considered MCI or Demented). The assumption of proportional hazards was tested for all models. If the assumption was not met, an interaction between a variable and the natural logarithm of time was included in the model to allow for the hazard to change over time. All analyses were conducted in SAS version 9.3 and a p-value < .05 was considered statistically significant.

Results

Informant-rated functional limitations predict incident MCI

Results examining the associated risk between baseline informant-rated ECog Total and domain scores and subsequent diagnostic conversion to MCI are presented in Table 4. In simple models adjusting for age and education, we found that older adults with higher baseline ECog Total scores, reflecting greater functional limitations, were at a greater risk of developing MCI at follow-up (a one unit increase on the ECog total was associated with a two-fold increased risk of converting to MCI). The greatest risk of converting to MCI at follow-up was associated with greater baseline limitations in Everyday Memory, Everyday Planning, Everyday Organization, and Everyday Divided Attention (a one-unit increase was associated with approximately a two-fold increased risk of converting to MCI). The latter three domains reflect aspects of everyday executive function. Everyday Language and Everyday Visuospatial were not significantly associated with conversion to MCI. Results were similar after removing those reclassified as NC (data not shown).

A second set of models controlled for baseline objective neuropsychological performance in memory and executive function (and age and education). The magnitude of the association between baseline ECog Total and the risk for subsequent diagnostic conversion to MCI was slightly attenuated, but remained significant. The risk associated with converting to MCI at follow-up based on baseline scores in the domains of Everyday Planning, Everyday Organization, and Everyday Divided Attention appeared less affected by the adjustment of neuropsychological performance. However, baseline scores in Everyday Memory and Everyday Planning remained significantly associated with the risk of converting to MCI at follow-up, even after controlling for baseline neuropsychological performance. Results were similar after removing those reclassified as NC, except that Everyday Divided Attention was no longer quite significant as a predictor (HR=1.6, 95% CI=.99–2.7, p=.055).

Self-rated functional limitations predict incident MCI

Regarding self-report measures, a one unit-increase on the self-reported ECog Total score (controlling for age and education) was associated with over a two-fold increased risk of conversion to MCI (Table 4). Unlike the unadjusted models using the informant-reported ECog scores, all six domains of the self-reported ECog scale were significantly associated with conversion to MCI (Table 4); Everyday Divided Attention had the smallest effect, while all other domains were closer to a two-fold increase risk of conversion. Results were similar after removing those reclassified as NC, except for Everyday Visuospatial (HR=1.7, 95% CI +.95–3.0, p=.07).

After adjusting for baseline neuropsychological test scores (and age and education), ECog Total, Everyday Memory, and Everyday Divided Attention remained significantly associated with conversion to MCI (Table 4). There were fewer self-reported ECog domains significantly associated with elevated risk for MCI once including the neuropsychological variables, as compared to the informant-rated ECog domains. The association was slightly attenuated for Everyday Memory and the ECog Total, but remained similar for Everyday Divided Attention.

Discussion

Among CN older adults prospectively followed over time, initial reports of subtle changes in everyday functional abilities substantially increase risk of subsequently developing MCI. These results add to a growing body of literature showing that changes in real-world abilities are among the first clinical signs of an incipient neurodegenerative disease.[21,47]

We examined whether the predictive utility of early functional changes varied by rater. Mild decrements in functional abilities predicted incident MCI regardless of whether ratings were based on self- or informant-report. Specifically, a one-unit increase in the ECog Total score (e.g., going from ‘no change’ in functional ability to occasionally performing worse) based on informant ratings was associated with a two-fold increase in risk of developing MCI over an average of 3 years. The self-reported ECog Total score was associated with a similar, although slightly higher risk ratio for incident MCI. This study is among the first to directly compare the value of self and informant-rated functional limitations in predicting risk of developing MCI and suggests that self-report is a strong predictor. Results of this study are consistent with the growing body of literature that demonstrate that subjective concerns regarding functional changes can be associated with biological markers of Alzheimer’s disease and related disorders including greater amyloid burden,[48,49] greater brain atrophy[50] and increased risk of incident dementia.[40]

Unique to this study, we examined what types of functional limitations predicted incident MCI. When examining informant-based functional ratings, as hypothesized, functional limitations in everyday memory and executive functions conferred the greatest risk for developing MCI. The ECog domain of Everyday Memory was associated with the highest risk and this domain alone performed as well as the ECog Total score. Such findings are not unexpected given that memory deficits are the hallmark symptom of AD and therefore, memory changes manifested in daily life are likely to be a harbinger of early AD. Poorer informant ratings of everyday executive domains with a similar relative risk included Everyday Organization and Everyday Planning. Everyday Organizational abilities include being able to structure ones’ environment to allow for maximum efficiency and manage important tasks (e.g., finances) in a timely and error-free manner. Everyday Planning refers to the ability to think ahead, anticipate possible hurdles, and sequence ones’ actions in an efficient way. The everyday executive domains have previously been identified as strong predictors of loss of independence in IADLs in NC individuals or those with MCI.[18] The current findings further highlight the importance of everyday executive functions as an early warning of a neurodegenerative disease and risk for eventual loss of autonomy.

When examining the types of *self*-reported functional limitations associated with incident MCI, a somewhat different pattern of results emerged. In this case all of the ECog domains were associated with a similar level of risk. The most striking difference was that the Everyday Language and Everyday Visuospatial domains were predictive of incident MCI when using self-report but not informant report. This discrepancy may be due to the relatively internal processes that are assessed by these domains and are thus more difficult for others to perceive. Everyday Language assesses ones' ability to utilize language to successfully comprehend new information and formulate and communicate ones' thoughts which may be less apparent to outside viewers, particularly if the person in question has developed compensation strategies to hide their weaknesses. The Everyday Visuospatial domain assesses geographic navigation ability (e.g., "following a map to a new location"). If a person is still driving independently, as would be presumed given their status as NC, it is less likely that these areas of difficulty will be apparent to an observer.

Detailed neuropsychological test results are often not available when patients initially start to express concerns about changes in their ability to perform complex functional tasks and so understanding the predictive value of functional complaints while not considering cognitive performance is of value. However, we were also interested in evaluating the degree to which reports of functional changes are of utility in predicting incident MCI when cognitive performance is considered. The influence of informant-reported functional limitations on incident MCI was, for the most part, not attenuated by baseline cognitive performance scores. Additionally, the overall pattern of results between the individual ECog domains and MCI conversion was similar. As such, even in the context of knowing cognitive test results, greater functional limitations as reported by a knowledgeable informant independently contributed to predicting the development of MCI. There was, perhaps, a slightly greater effect of including baseline cognition on the impact of self-reported functional limitations and incident MCI. Overall, when cognitive performance was included in the model, fewer self-rated ECog domains remain predictive of MCI conversion. However, the magnitude of the effect of self-reported functional limitations on incident MCI when using the ECog Total was the same as when the informant-reported ECog Total was used. Overall, the current results provide evidence that subtle functional limitations, through self- or informant-report, increases risk of developing MCI independent of the effect of cognitive test performance.

Study strengths and limitations

Participants of this study were part of a well characterized cohort all of whom undergo a comprehensive diagnostic evaluation annually and are diverse in terms of demographic factors and background. Nonetheless, older adults who volunteer to participate in research may be different than the general population, potentially limiting generalizability. While those who converted to MCI over follow-up were shown to have slightly lower cognitive scores at study baseline, they had all undergone extensive neuropsychological testing to confirm their NC status. Further, cognitive and functional tests used for diagnostic purposes were distinct from the tests used as predictors or outcomes in the present study. Finally, functional assessment was based on self- and informant-report and both are subject to reporting biases. However, the similarity in findings across raters increases our confidence in the results. Previous studies also showed ECog ratings to relate to objective biomarkers.[9]

Clinical implications and Future Directions

Results of this study suggest that it is important for clinicians to take concerns about subtle changes in everyday function seriously, whether reported by the patient or a knowledgeable informant. Such concerns substantially increase an older adult's risk that they will develop MCI within a few years. Generally speaking, clinicians should inquire about how older adults are functioning in their daily life particularly with regard to tasks heavily dependent on memory (e.g., remembering appointments) and executive functions (e.g. organization). The presence of such subtle changes should serve to trigger either further work-up or enhanced monitoring over time. Results suggest the ECog, in particular, may be a useful instrument to help to screen for risk of MCI. Our previous work suggests that measurement of functional abilities may be particularly helpful among older adults from diverse backgrounds, with low education, or where English is not their primary language.[20] In future work, it will be important to more specifically examine the predictive utility of the ECog across ethnically and educationally diverse older adult populations.

Acknowledgments

Grant funding: AG10129 and AG031252

Sponsor's Role

The sponsor (National Institute on Aging) provided funding for all aspects of study.

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Table 1

Baseline demographic characteristics (mean (standard deviation) unless otherwise noted).

Variables	**Total (*n* = 324)**	**Stable Normal (n=264)**	**Converters to MCI (n=60)**	***p***
Age	75.5 (6.9)	74.9 (6.8)	78.0 (7.1)	.002
Education	13.9 (3.7)	14.0 (3.7)	13.3 (3.7)	.2
Female [N (%)]	205 (63.3)	168 (63.6)	37 (61.7)	.8
Race/Ethnicity [N (%)]				.3
African American	77 (23.8)	63 (23.9)	14 (23.3)	
Caucasian	154 (47.5)	128 (48.5)	26 (43.3)	
Hispanic	69 (21.3)	53 (20.1)	16 (26.7)	
Other/Unknown	24 (7.4)	20 (7.6)	4 (6.7)	

Table 2

ECog domain and total scores, and cognitive functioning (mean (standard deviation) unless otherwise noted).

Variables	Total (n = 324)	Stable Normal (n=264)	Converters to MCI (n=60)	p
MMSE	28.1 (1.9)	28.2 (1.8)	27.3 (2.3)	.007
Everyday Memory-informant	1.60 (.61)	1.55 (.60)	1.83 (.63)	<.001
Everyday Language-informant	1.35 (.50)	1.33 (.49)	1.45 (.52)	.052
Everyday Visuospatial-informant	1.26 (.46)	1.26 (.48)	1.31 (.38)	.03
Everyday Organization-informant	1.36 (.54)	1.33 (.50)	1.50 (.68)	.15
Everyday Planning-informant	1.25 (.44)	1.23 (.43)	1.34 (.48)	.08
Everyday Divided Attention-informant	1.50 (.66)	1.45 (.62)	1.73 (.79)	.01
ECog Total Score-informant	1.40 (.46)	1.37 (.46)	1.53 (.46)	.002
Everyday Memory-self	1.72 (.67)	1.66 (.62)	1.99 (.78)	.001
Everyday Language-self	1.50 (.57)	1.46 (.53)	1.67 (.70)	.03
Everyday Visuospatial-self	1.28 (.46)	1.25 (.41)	1.41 (.62)	.14
Everyday Organization-self	1.41 (.55)	1.38 (.55)	1.51 (.56)	.04
Everyday Planning-self	1.26 (.45)	1.24 (.45)	1.35 (.44)	.02
Everyday Divided Attention-self	1.56 (.71)	1.51 (.69)	1.73 (.76)	.02
ECog Total Score-self	1.46 (.47)	1.42 (.44)	1.63 (.55)	.004
SENAS Episodic Memory[1]	.2 (.8)	.3 (.7)	−.2 (.7)	<.001
SENAS Executive Function[2]	.04 (.59)	.1 (.6)	−.2 (.6)	.008
Time to incident MCI or last assessment (years)	3.9 (2.4)	4.2 (2.4)	3.0 (2.1)	<.001

Note: ECog = Everyday Cognition Scale; MCI = Mild Cognitive Impairment; MMSE = Mini-Mental State Exam; SENAS = Spanish English Bilingual Neuropsychological Assessment Scales.

[1] Available for 218 participants (172 stable, 46 converters),

[2] Available for 221 participants (175 stable, 46 converters)

Table 3

Example ECog items.

ECog Items	Examples
Everyday Memory	Remembering a few shopping items without a list; remembering appointments or meetings.
Everyday Language	Forgetting the names of objects; communicating thoughts in conversation.
Everyday Visual Perception	Following a map to find a new location; Finding the way back to a meeting spot in a mall.
Everyday Planning	Planning a big dinner, social event, birthday party, or club meeting; Planning a recreational outing.
Everyday Organization	Keeping living and work space organized; Assembling business, tax or financial records.
Everyday Divided Attention	Carrying on a conversation when the TV is on in the room or while other people are talking; Keeping track of multiple things while cooking.

Table 4

Associations between ECog domain and total scores at baseline, and diagnostic conversion to MCI at follow-up.

	ECog models[a]		ECog and cognition models[b]	
Independent variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Everyday Memory - informant	2.0 (1.4–2.9)	<.001	1.8 (1.2–2.9)	.006
Everyday Language - informant	1.5 (.9–2.4)	.12	1.3 (.7–2.4)	.46
Everyday Visuospatial - informant	1.4 (.8–2.4)	.18	1.1 (.6–2.2)	.69
Everyday Planning - informant	1.8 (1.1–3.1)	.02	2.0 (1.1–3.6)	.03
Everyday Organization - informant	1.9 (1.3–2.8)	.001	1.9 (1.1–3.0)	.01
Everyday Divided Attention - informant	1.7 (1.2–2.4)[c]	.001	1.7 (1.1–2.7)	.02
ECog Total Score - informant	2.0 (1.3–3.2)	.002	1.9 (1.1–3.2)	.02
Everyday Memory - self	1.9 (1.3–2.6)	<.001	1.6 (1.1–2.4)	.02
Everyday Language - self	1.8 (1.2–2.7)	.003	1.6 (.9–2.6)	.10
Everyday Visuospatial - self	1.8 (1.1–2.9)	.03	1.6 (.9–2.8)	.10
Everyday Planning - self	1.8 (1.1–3.0)	.01	1.6 (.8–3.0)	.17
Everyday Organization - self	1.9 (1.2–2.9)	.003	1.4 (.8–2.4)	.21
Everyday Divided Attention - self	1.6 (1.1–2.3)	.006	1.7 (1.1–2.5)	.01
ECog Total Score - self	2.3 (1.4–3.6)	<.001	1.9 (1.1–3.4)	.03

Note: ECog = Everyday Cognition Scales; CI = confident interval; HR = hazard ratio.

[a]Model adjusted for age, education and baseline ECog domain or total score.

[b]Model adjusted for age, education, baseline ECog domain or total score, and cognitive functioning (memory and executive functions)

[c]The assumption of proportional hazards is not met in this model (p=.03). When an interaction between baseline Everyday Divided Attention and logarithm of time is included in the model, the estimated hazard ratio is higher at early time points and lower at later time points (i.e., the hazard ratio decreases over time).