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Self-rated and informant-rated everyday function in comparison to objective markers of Alzheimer's disease

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Abstract

It is recognized that individuals with mild cognitive impairment (MCI) already demonstrate difficulty in aspects of daily functioning, which predicts disease progression. This study examined the relationship between self- versus informant-report of functional ability, and how those reports relate to objective disease measures across the disease spectrum (i.e. cognitively normal, MCI, Alzheimer's disease). A total of 1,080 subjects with self- and/or informant-rated Everyday Cognition (ECog) questionnaires were included. Objective measures included cognitive functioning, structural brain atrophy, cerebrospinal fluid (CSF) abnormalities, and a marker of amyloid deposition using positron emission tomography (PET) with [^{18}F]AV45 (florbetapir).

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Overall, informant-report was consistently more associated with objective markers of disease than self-report although self-reported functional status may still have some utility in early disease.

Keywords

mild cognitive impairment (MCI); Alzheimer's disease; dementia; everyday function; daily functioning; instrumental activities of daily living; informant-report; self-report; biomarkers; ADNI

1. Introduction

There is considerable interest in identifying the prodromal clinical signs of Alzheimer's disease (AD). While loss of independence in everyday functional abilities is a core feature of AD dementia, there is increasing recognition that mild functional changes occur early in the disease, including within Mild Cognitive Impairment (MCI) (1–3). New evidence suggests subtle functional changes may be detected in individuals who are still considered cognitively normal (4). Early detection of functional decline has prognostic value in predicting future disease progression (5).

Past research on functional changes in preclinical AD has been hindered by a lack of instruments sensitive to early and subtle functional problems. The Everyday Cognition (ECog) is a newer instrument designed to assess functional abilities linked to specific cognitive abilities and, it has been shown to be sensitive to early disease (2, 6). While the utility of *self*-report on the ECog has not yet been specifically evaluated, previous studies have suggested that early self-reported changes in everyday functioning may be associated with development of MCI or dementia (7, 8).

Approaches to assessing the validity of self-report include comparing self- and informant-reports, and evaluating associations between self-report and objective measures of disease. In general, the degree to which individuals with early disease, such as MCI, can accurately report cognitive and functional problems remains unclear. Some studies report a lack of difference between self- and informant-ratings in MCI (3, 9, 10), suggesting that individuals may retain the ability to accurately report functional status. Other studies, however, have questioned the usefulness of self-reported functional change in MCI due to its discrepancy with informant-ratings (11, 12). In dementia, self-reported functional status is often inaccurate due to loss of awareness/insight (10, 13).

Self- and informant-ratings of everyday functioning in MCI and prodromal AD have been compared to objective cognitive tests. The correspondence between self-reported everyday function and cognition is inconsistent; some studies show no relationship (14, 15) while others have found that subjective everyday cognitive complaints among elderly individuals are associated with cognitive performances (16, 17). More consistent associations have been reported between *informant*-ratings of reduced everyday function and cognition (1, 5, 18–20). When self- and informant-ratings were concurrently compared with neuropsychological performance, the latter ratings have been more strongly associated with objective cognitive testing (10, 21).

Ratings of everyday functioning have also been compared to other biomarkers of disease. For instance, informant-reports of functional decline have been associated with structural abnormalities on imaging, including decreased cortical gray matter (22) and smaller hippocampal volume (1), as well as neuropathological abnormalities in MCI, such as elevated concentrations of total tau (t-tau) (23), reduced Aβ 1–42 in CSF (23), and increased amyloid deposition on Pittsburgh compound B positron tomography (PiB-PET) (24). Considerably less work has examined *self*-reported functional decline and associated disease biomarkers. There is some evidence that elderly individuals with subjective cognitive complaints and normal cognitive test performances exhibit reduced medial temporal and frontotemporal gray matter volumes similar to individuals with MCI (14) and increased amyloid-β deposition on PiB-PET imaging (7, 25). Such findings suggest self-appraisals may be sensitive to underlying early neuropathologic changes when objective cognitive impairments may be less apparent.

In sum, informant-reported everyday function has been previously associated with a number of disease related outcomes in MCI and dementia. The validity of self-reported functional decline across the full disease spectrum, particularly among older adults with normal cognition or MCI, is less clear. The present study used a variety of approaches to examine the relative validity of self- and informant-reported functional status among individuals defined as Normals, early MCI (EMCI), late MCI (LMCI), and Alzheimer's dementia (AD). Specifically, we investigated (1) the degree of agreement between informant- and self-reported everyday functioning at different disease stages, (2) the utility of informant- and self-reported functional status in discriminating between diagnostic groups, and (3) the relationships between informant-and self-reported functional ability and multiple objective markers of disease. Generally, we hypothesized that while informant-reported functional status would be superior to self-report in all of these regards, self-report would have some demonstrable validity particularly in early disease.

2. Methods

2.1. Participants

Data was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a consortium of university and medical centers in the United States and Canada aimed to study changes in cognition, function, brain structure, and biomarkers in cognitively normal and subjects with MCI and AD (26). The present study included 1,080 subjects with self-rated and/or an informant-rated ECog (see Table 1). Subjects were diagnosed based on the following criteria: MCI was diagnosed based on subjective memory complaints, objective memory impairment measured by education-adjusted scores falling at least 1.5 standard deviations below the normative mean on delayed recall of the Logical Memory test (Story A), essentially independent for activities of daily living, global score of 0.5 on the Clinical Dementia Rating scale (CDR), and Mini-Mental state examination (MMSE) score ≥ 24. These subjects were subsequently characterized as LMCI and differentiated from a new group of EMCI subjects recruited during the second phase of ADNI (ADNI-GO/ADNI-2). EMCI was characterized by milder episodic memory impairments with scores on delayed recall of the Logical Memory test falling between 1.0 to 1.5 standard deviations below an

education-adjusted normative mean, (27). By design, the ADNI MCI cohort is memory impaired compared to Normals, but with better memory performance than those with AD, and are more similar to Normals in non-memory domains than they are to those with AD (26). These MCI groups represent the transitional stage between normal aging and clinical criteria for probable AD (26). Subjects with AD had MMSE scores between 20 and 26 (inclusive), CDR global scores of 0.5 to 1.0, and met criteria for probable AD according to the National Institute of the Neurological and Communicative Diseases and Stroke-Alzheimer's disease and Related Disorders Association (NINCDS/ADRDA) (28).

2.2. Assessment of everyday function

The Everyday Cognition (ECog) questionnaire measures cognitively-relevant functional abilities across six domains: Everyday Memory, Language, Visuospatial abilities, Planning, Organization, and Divided Attention. The present study used a global score reflecting a composite of all six domains (7). The ECog contains a total of 39 items, which are rated on a four-point scale: 1 = better or no change compared to 10 years earlier, 2 = questionable/occasionally worse, 3 = consistently a little worse, 4 = consistently much worse. Higher scores indicate greater functional impairment. To allow for missing data, an average was calculated by summing scores of completed items and dividing by the number of completed items.

The ECog was designed to capture relatively mild functional changes that likely predate loss of independence in major activities of daily living (ADLs). The ECog has been shown to be sensitive to early functional changes seen in MCI as well as dementia (2, 4, 6). The ECog has been shown to have excellent internal reliability (Cronbach's alpha = 0.97) as well as good test re-test reliability ($r=.82$, $p<.001$) (6). Various aspects of validity have been demonstrated via its correlation with other well-known measures of daily function (6), as well as cognitive and neuroimaging indicators of disease (6, 29). Finally, the ECog has been shown to be sensitive to change over time and shows differential rates of change in relation to baseline diagnosis and change in diagnosis over follow-up (4).

2.3. Neuropsychological measures

The ADNI neuropsychological battery is detailed elsewhere (26). The reliability and validity of these tests has been previously established (30). Within this battery, we focused on memory and executive function due to previous findings that consistently reported relationships between these abilities and everyday functioning (4, 18, 31–33). Memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT) (34). The RAVLT is a 15-word list-learning task, administered for five consecutive trials, followed by presentation of an interference list, and recall of the original list. A 20-minute delayed recall trial is also administered. The RAVLT memory variables used in the current analyses included total recall from the five learning trials and from the 20-minute delay. Executive functioning, specifically mental flexibility and cognitive switching, was measured using the Trail Making Test – Part B (TMT-B) (35), which was scored as the total time of completion.

2.4. Structural Neuroimaging

Participants received brain MRI scans using a 3T scanner. Specific protocols are described elsewhere (36, 37). Volumetric quantifications were obtained using a semi-automated, 3-D whole-brain segmentation/parcellation packaged (FreeSurfer, Version 5.1). For the current analyses, total ventricular (a composite measure of all ventricles reflecting global atrophy) and hippocampal volumes were used. Neuroimaging obtained within 180 days of the ECog ratings was used in the present study.

2.5. CSF collection and analyses

Cerebrospinal fluid (CSF) samples were collected, and Aβ 1–42 and p-tau were measured based on standardized protocols outlined by the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center (38). Extracellular deposition of amyloid beta (Aβ) is a defining lesion of AD. It is thought that Aβ 1–42, the least soluble of amyloid beta peptides, is amongst the most promising and informative AD biomarkers (40). A reduction in CSF Aβ 1–42 has been hypothesized to indirectly reflect the amyloid deposition in senile plaques (39, 40). Elevated CSF phosphorylated tau (p-tau) levels reflect abnormal tau accumulation found in neurofibrillary tangles (40).

2.6. Florbetapir PET scans

PET imaging using [^{18}F]AV45 (florbetapir) was performed based on the following procedures. Participants received a bolus intravenous injection of approximately 370MBq of [^{18}F]AV45. After a 50-minute uptake period, a 20-minute cranial PET scan was initiated. PET images were reconstructed immediately following the scan using iterative algorithms, and repeat scans were acquired if motion artifact was detected. Preprocessing of the scans was performed as previously described (41).

2.7. Data analyses

Analysis of variance and chi-square tests were used to compare demographics and basic clinical features of the diagnostic groups. Post-hoc pairwise comparisons for specific group differences were adjusted for multiple comparisons using the Bonferroni correction. To address the first goal of this study, the signed rank test was used to compare self-reported to informant-ratings of the ECog across all subjects as well as within diagnostic groups. Further, to compare the ECog across diagnostic groups within a rating type, the ECog was first transformed using the natural log. Due to the restricted range (1–4 on the raw scale and 0-ln(4) on the transformed scale) and high frequency of values near the lower bound, a tobit regression model with a lower bound of zero was used adjusting for age, gender, and APOE4 status. Contrasts were constructed to compare the different diagnostic groups and p-values were adjusted using the Bonferroni correction. Receiver operating characteristic curves (ROC) and the non-parametric estimate of the area under the ROC (AUC) based on the trapezoidal rule were used to evaluate the accuracy of predicting diagnosis groups using the ECog Informant and Self reports (the second goal of the study). Particular comparisons of interest were structured in a hierarchical manner, comparing groups with more impairment to groups with no or less impairment. Specifically, Normals were compared to each of the other diagnostic groups (EMCI, LMCI, AD), EMCI were compared to each of

the more impaired groups (LMCI, AD), and LMCI was compared to AD. In addition, any impairment (EMCI, LMCI, or AD) was compared to Normals. For each analysis, the specificity corresponding to a sensitivity of 80% is reported as the optimal cut-off score for that same sensitivity. To address the final goal of the study, partial Spearman rho correlations were computed, partialling out age, gender and APOE status, to analyze the relationships between the ECog ratings (self- and informant-ratings) and neuropsychological measures, MRI measures, and CSF variables across the entire group (all diagnoses combined) and within diagnostic groups. Due to the large number of correlations, False Discovery Rate, a method that controls the expected proportion of falsely rejected hypotheses (42), was used to adjust for multiple comparisons. All analyses were done using SAS 9.3 (SAS Institute, Cary, NC).

3. Results

3.1. Sample characteristics

In the entire sample, the mean age was 76.3 (SD = 8.0), 44.5% were female, and the mean education in years was 16.11 (SD = 2.72). The majority of the sample was Caucasian (88.7%). Table 1 details demographic and clinical variables for each of the four diagnostic groups. Normal, LMCI, and AD groups were significantly older than the EMCI group (corrected $p < .001$). Normals had a higher percentage of females than the LMCI and AD groups, although not quite significant after adjustment for multiple comparisons (corrected $p = .08$). All groups differed on MMSE with Normals having the highest scores and AD having the lowest scores (corrected $p < .001$). The EMCI and LMCI groups had similar *APOE* ε4 positivity rates (raw p =.22), while all other groups differed (corrected $p < .002$).

3.2. Agreement between informant and self-report across diagnostic groups

There was no significant difference between informant- and self-ratings on the ECog (raw p =.08) in the pooled sample (all diagnostic groups combined). When looking at differences in ECog self- and informant-ratings amongst diagnostic groups (Table 2), Normals and EMCI rated themselves as having slightly *worse* everyday function (higher scores) compared to informant ratings (corrected $p < .001$; Cohen's d is .59 and .28, respectively). The AD group rated themselves as *less* functionally impaired (lower scores) than did their informants (corrected $p < .001$; Cohen's d=1.4). While self-ratings of functional abilities among LMCI were also slightly less (indicating less impairment) than informant-reports, these ratings were not significantly different ($p = .27$; Cohen's d=.12).

When looking at self-reported daily functioning across diagnostic groups, the expected pattern emerged. Greater functional impairment was reported with increased disease severity. This pattern may suggest some preserved recognition of functional difficulties. The same pattern held true for informant ratings. When examining informant-rated ECog, all group comparisons were significantly different (corrected p <.0001). Normals had better everyday function than all other groups, EMCI had less functional impairment than LMCI and AD, and LMCI had less functional impairment than AD. For the self-report ECog scores, Normals reported better everyday function than EMCI, LMCI, and AD (corrected p

<.0001), but the EMCI group had equivalent ECog ratings to LMCI (raw p = .60) and AD (raw p = .24). LMCI and AD groups had similar mean ECog scores (raw p = .51).

3.3. Utility of informant- and self-report to discriminate diagnostic groups

Table 3 summarizes the ROC curve analysis with specificity (at 80% of sensitivity) for each diagnostic comparison. Informant-report consistently provided better group discrimination than self-report. Self-report was not much better than chance in distinguishing AD from EMCI (AUC = .53) or LMCI (AUC = .52). Informant- or self-report methods were also not very good at discriminating between the LMCI and EMCI groups, although informant-report was slightly better than self-report (informant-report: AUC=.62; self-report: AUC=.51). If age, gender, and APOE4 status are included in the model, the AUC increases by .01−.04 for the informant rating and by .03−.19, with the highest increases in the comparisons between the non-Normal groups for the self-report (data not shown since most often genetic status is not known in clinical settings).

3.4. The relationship between the ECog and neuropsychological outcomes

For the combined sample, informant- and self-ratings of everyday function were significantly correlated with measures of memory and executive functioning (cognitive flexibility and switching). Specifically, fewer items recalled on the RAVLT total learning and delayed recall trials, and longer time to completion on TMT-B were associated with worse everyday function (higher ECog scores). Self-ratings were less strongly associated with memory and aspects of executive functioning than informant ratings (Table 4).

Correlations between self- and informant-reported ECog and neuropsychological variables were also examined for each diagnostic group. Informant ratings on the ECog were fairly consistently correlated with measures of memory and executive function within diagnostic groups; the strongest associations were found in the LMCI and AD groups. Alternatively, for self-report, the correlations were small and in most cases, not statistically significant within diagnostic groups.

3.5. The relationship between the ECog and structural neuroimaging

In the entire sample, informant- and self-reported ECog scores were significantly associated with total ventricular and hippocampal volumes, although the strength of the associations between informant-rated function and brain volumes were stronger than those observed with the self-reported ECog ratings. In both cases, worse everyday function was associated with greater ventricular size (positive correlations) and smaller hippocampi (negative correlations), reflecting more brain atrophy. For informant and self-reports, everyday function tended to be somewhat more strongly related to hippocampal volume than ventricular volume (Table 4).

When examining the association between self- and informant-reported everyday function and brain volumes among diagnostic groups, the strength of the associations tended to be higher for the informant ratings. There was minimal association between self-reported everyday function and brain volumes when examining diagnostic groups separately, with the

exception of a small association between hippocampal volume and self-reported ECog in the EMCI group (statistically significant at the .05 alpha level only).

3.6. The relationship between the ECog and CSF biomarkers of Alzheimer's disease

In the combined sample, informants' report of worse everyday functioning on the ECog was significantly associated with higher p-tau and lower Aβ 1–42. Self-ratings of greater functional impairment were associated with lower Aβ 1–42 levels, but p-tau levels (Table 4). When we stratified analyses by diagnostic groups, informant-rated everyday function continued to be more strongly associated with the CSF biomarkers among the diagnostic groups than the self-reported ECog scores. In particular, there was a modest association between p-tau and the informant-rated ECog in the LMCI group. Self-rated ECog scores showed non-significant associations with CSF biomarkers.

3.7. The relationship between the ECog and PET imaging

A positive correlation was observed between informant ratings and [^{18}F]AV45. Greater difficulty with daily function was associated with greater amyloid deposition in the entire sample. Self-report of greater functional impairment was also significantly associated with greater [^{18}F]AV45 retention in the entire sample, but to a lesser degree (Table 4). Analyses stratified by diagnostic groups revealed an association between informant-report of everyday functioning and amyloid load in the LMCI group. Self-rated ECog scores were not significantly associated with [^{18}F]AV45 retention.

4. Discussion

The present study examined the relative validity of self- and informant-reported functional status across a wide spectrum of disease, including individuals with normal cognition, MCI, and dementia. Unique to the current ADNI cohort, the heterogeneous category of MCI has been further subdivided into early and late MCI based on degree of memory impairment. This allowed us to assess everyday function at varying stages of MCI/memory impairment.

First, we assessed the validity of self-report by comparing it to reports of other raters familiar with the participant. Dementia participants rated themselves as *less* functionally impaired when compared to their informants' ratings, which is consistent with previous literature (10). Taken together with stronger correlations between informant ratings and objective measures of disease, these results likely reflect decreased insight in individuals with dementia (10). A more complex pattern emerged when we examined rater differences across the MCI groups. There was also a tendency for individuals within the LMCI group to report *less* functional impairment than informants. Alternatively, the EMCI and cognitively normal participants rated themselves as having slightly *more* problems with everyday function compared to their informants. Interestingly, the EMCI group showed a similar pattern of reporting to Normals and different from LMCI and dementia, possibly suggesting that individuals in the early part of MCI may be more reliable in assessing their functional capacities. As disease progresses into later stages of MCI, individual's report of functional abilities may become more tenuous. Previous studies comparing self- and informant-reported functional capacities among individuals with MCI have been mixed (3, 9, 10, 31),

and the present results may help explain some of this variability in that reporting may depend on the degree of memory impairment in MCI. However, when we formally compared the ability of informant and self-reported functional ability to discriminate between clinical/diagnostic groups, informant-ratings are clearly superior. Even in EMCI, self-reported everyday function correlates minimally with objective disease markers. Overall, such findings highlight the importance of informant report in clinical and research settings. In particular, informant report is highly effective in differentiating normal older adults from those with dementia. Informant ratings also fairly strongly discriminated between traditional MCI (LMCI) and normal elderly - an important objective. However, informant-report of functional status is limited in making more fine group discriminations, such as distinguishing Normals from EMCI, and EMCI versus LMCI.

Self- and-informant reports of everyday functions were also examined with respect to various objective markers of disease. In terms of cognitive functioning, our finding that informant-ratings of everyday function had consistently stronger relationships with memory and executive functions (e.g. cognitive flexibility, switching) than self-reports is consistent with previous studies (18–20). Self-ratings of everyday function had weaker and mostly, non-significant associations with neuropsychological test scores within diagnostic groups. In contrast to what we expected, self-reported functional status was not more related to neuropsychological performance in Normals or EMCI as compared to the LMCI and AD dementia groups. It is worth noting that among Normals, the magnitude of associations between the ECog and neuropsychological function (e.g. delayed recall), albeit weak, was similar between raters, perhaps suggesting that self-report of subtle functional changes in this subgroup may be associated with cognitive performance. Emerging research examining the relationships between subjective cognitive and functional complaints and objective cognitive measures among normal elderly individuals has also yielded mixed results or similarly weak relationships (43, 44). However, longitudinal studies suggest early cognitive complaints may help to predict subsequent decline in cognition or otherwise help identify a high risk group (45).

With regard to structural neuroimaging, worse informant-rated functional ability was associated with both global brain atrophy via larger ventricular volume as well as greater hippocampal atrophy, with the latter relationship being somewhat stronger. Results are consistent with other studies, indicating correlations between functional impairments and widespread brain atrophy (20, 22, 46) and regional atrophy in the hippocampus (1, 9). Hippocampal atrophy is an early sign of AD (47), suggesting a link between early brain changes and early functional consequences. Examination of the diagnostic groups suggested that informant reported everyday function is most strongly associated with atrophy among those with MCI. The lack of relationship between everyday function and structural neuroimaging measures among Normals is not entirely inconsistent with previous studies which have revealed mixed findings with regard to associations between everyday cognitive complaints and structural brain imaging in cognitively normal elderly (14), (17). Taken together, weak and inconsistent associations with self-report seem to be the case.

There is considerable interest in determining whether novel biomarkers of AD-related pathology relate to everyday cognitive/functional reports, particularly among those still

cognitively normal (44). In the present study, we examined beta amyloid measured from CSF and [^{18}F]AV45 PET imaging. Lower CSF Aβ 1–42 concentrations and higher [^{18}F]AV45 retention, reflecting higher amyloid accumulation in the brain, were associated with worse everyday functioning within the entire sample using informant and self-reports, although informant-report consistently demonstrated a more robust association. Within diagnostic groups, analyses did not reveal significant associations between CSF Aβ 1–42 and everyday functioning for either rater. Informant-rated, but not self-reported, everyday functioning was significantly related to [^{18}F]AV45 retention among the EMCI and LMCI groups. Previous research using PiB retention also showed similar findings (24).

When the association between everyday function and p-tau was examined, self-reported ECog scores were not associated with p-tau in the entire sample or within diagnostic groups. Informant-report of worse functional status was related to higher levels of p-tau in the whole sample, and particularly within the LMCI group. A previous study also found significant associations of p-tau, as well as t-tau and Aβ 42, with informant-rated functional decline in MCI but not in AD (23). Those authors speculated that once CSF biomarkers become abnormal, they tend to remain stable for several years, which may reduce variability in CSF biomarkers.

To our knowledge, this is the most comprehensive study to date examining self- versus informant-report in comparison to multiple objective cognitive and biological markers of disease in a moderately large sample of well-characterized individuals, representing a wide spectrum of disease. However, there are a number of limitations to this study. The ADNI cohort is predominantly Caucasian (88%), more highly educated than the general U.S. older adult population, and is comprised of self-selected participants who have a higher genetic risk for the development of AD (e.g. higher prevalence of *APOE* ε4) than the general population (26). As such, results may not generalize to other population-based samples. Given that the MCI sample was selected based upon their memory impairment, our findings may not generalize to other MCI subtypes. Additionally, we used ECog total scores, which may have masked subtle differences across domains of daily functioning. Informant and self-reports of everyday function are both subject to a number of biases as compared to performance-based measures. As already noted, limitations in awareness of deficits that occur in dementia and even MCI reduce validity of results. Factors, such as elevated caregiver burden and depression among caregivers, have also been shown to affect informant reports of patient functioning (48, 49). Performance-based measures are subject to their own limitations and are often impractical to use, but there is some evidence that they may be more sensitive to discriminating diagnostic groups that subjective ratings (50).

In summary, the primary finding of this study is that informant-reported everyday function is consistently more strongly related to multiple indicators of disease - including brain atrophy, neuropathologic abnormalities, and neuropsychological test performance - than self-report. Such findings highlight the importance of obtaining collateral report, and suggest that when discrepancies across raters occur, strong weight should be placed on the ratings made by knowledgeable informants. It is important to note that group-level findings often present challenges when attempting to apply them to individual cases where insight and reliability of self-report can sometimes be preserved, even in individuals with clear cognitive

impairment. In clinical settings where maintenance of autonomy is a high priority, one approach that could be employed when discrepancies are observed between self- and informant/caregiver-report is to then administer more objective, performance-based measures of functional abilities. It is important to keep in mind that the present study does not address the degree to which self-report, particularly in those still cognitively normal or only minimally impaired (e.g. EMCI), is associated with increased risk for subsequent cognitive or functional decline/disease progress and this is an important avenue of further study.

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Table 1

Demographic sample characteristics by diagnostic groups

		Normal (*n*=307)	EMCI (*n*=310)	LMCI (*n*=251)	AD (*n*=212)	Test Statistic	Test p-value
Age	*M*	77.94	73.21	76.68	77.81	23.84[1]	<.0001[1]
	SD	6.88	7.77	8.54	7.95		
Female	*N*	158	136	102	85	9.26[2]	.03[2]
	%	51.47	43.87	40.64	40.09		
Education	*M*	16.40	15.97	16.18	15.81	2.34[1]	.07[1]
	SD	2.63	2.67	2.85	2.76		
MMSE	*M*	29.04	28.32	27.62	22.37	536.44[1]	<.0001[1]
	SD	1.26	1.56	1.80	3.26		
APOE ε4[3]	*N*	79	131	122	138	83.56[2]	<.0001[2]
	%	25.99	43.23	48.80	66.03		

[1] ANOVA (F-test degrees of freedom (df)=3);

[2] Chi-square (df=3);

[3] *APOE* ε4 data was missing for 3 Normal, 7 EMCI, 1 LMCI, and 3 AD individuals.

Table 2

ECog total scores for informant-report and self-report across diagnostic groups

	Informant-ratings			Self-report			
Diagnostic group	***n***	***M***	***SD***	***n***	***M***	***SD***	***p-value*[1]**
Normal	300	1.17[2]	0.26	307	1.34[3]	0.31	<.0001
EMCI	305	1.64[2]	0.54	310	1.79	0.53	<.0001
LMCI	249	1.88[2]	0.64	251	1.81	0.54	.28
AD	211	2.82[2]	0.66	212	1.90	0.65	<.0001
Total	1,065	1.79	0.78	1,080	1.68	0.54	.08

Note: ECog=Everyday Cognition score; M=mean; SD=standard deviation

[1] p-value is for the comparison of the informant ratings to the self-report; the raw p-value is reported, but is significant after correction for multiple comparisons if p<.008

[2] All groups are significantly different from one another (corrected p<.0001); obtained from a tobit regression model adjusting for age, gender, and APOE4 status.

[3] Normals are significantly different from the other groups (corrected p<.0001), but other groups are similar (EMCI vs LMCI: p=.60; EMCI vs AD: p=.24; LMCI vs AD: p=.51); obtained from a tobit regression model adjusting for age, gender, and APOE4 status.

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Table 3

Receiver operating characteristic curve using ECog total score by informant-report and self-report

	Informant report			Self-report		
Diagnostic group comparisons	***n***	**AUC**	**Specificity at sensitivity = 80%**	***n***	**AUC**	**Specificity at sensitivity = 80%**
1 AD vs Normal	511	.99 (CI = .98−.99)	99%	519	.79 (CI = .74−.83)	60%
2 LMCI vs Normal	549	.88 (CI = .85−.91)	82%	558	.80 (CI = .77−.84)	64%
3 EMCI vs Normal	605	.83 (CI = .80−.86)	71%	617	.79 (CI = .75−.82)	62%
4 “Impaired” vs Normal	1065	.89 (CI = .87−.91)	82%	1080	.79 (CI = .76−.82)	62%
5 AD vs EMCI	516	.90 (CI = .88−.93)	89%	522	.53 (CI = .48−.58)	16%
6 LMCI vs EMCI	554	.62 (CI = .57−.66)	33%	561	.51 (CI = .46−.56)	23%
7 AD vs LMCI	460	.84 (CI = .80−.88)	76%	463	.52 (CI = .46−.57)	16%

Note: Impaired = AD + EMCI + LMCI groups; AUC=area under the curve; CI=95% confidence interval; ECog=Everyday Cognition score

Table 4

Partial Spearman rank correlations between ECog total score and neuropsychological, structural neuroimaging, CSF, and PET biomarkers, adjusted for age, gender and APOE4 status.

	Neuropsychological markers				Structural neuroimaging			CSF biomarkers(6)			[^{18}F]AV45 PET	
Diagnostic groups	***n***	**RAVLT Learning**	**RAVLT Recall**	**TMT-B**	***n***	**VV**	**HV**	***n***	**Aβ 1–42**	**p-tau**	***n***	**summary SUVR**
Informant-report												
Normals	297	−.05	−.12*	.09	189	.004	−.02	79	−.10	.13	251	.03
EMCI	301	−.05	−.17**	.06	299	.06	−.13*	104	−.14	.10	285	.09
LMCI	246	−.20**	−.27***	.27***	166	.07	−.21**	110	−.11	.23*	207	.26***
AD	206	−.21**	−.15*	.28***	126	.05	.01	102	−.02	−.05	141	−.06
Total Group	1,050	−.52***	−.53***	.43***	780	.19***	−.37***	395	−.34***	.25***	884	.29***
Self-report												
Normals	303	−.08	−.11	.04	193	.03	.07	79	−.004	−.13	254	−.04
EMCI	303	−.03	−.06	.07	301	.04	−.12*	106	−.07	−.01	287	.02
LMCI	248	−.04	−.02	.16**	166	.02	−.08	110	−.13	−.04	209	.07
AD	207	−.07	.07	.19**	127	−.05	.10	103	.09	.01	141	−.03
Total Group	1,061	−.25***	−.22***	.25***	787	.08*	−.18***	398	−.18***	.04	891	.13***

CSF = cerebrospinal fluid; HV = hippocampal volume; PET = positron emission tomography; RAVLT = Rey Auditory Verbal Learning Test; SUVR = standardized uptake value ratio; TMT-B = Trail Making Test Part B; VV = ventricular volume;

*** $p < .001$ (remained significant after multiple comparison adjustment),

** $p \leq .015$ (remained significant after multiple comparison adjustment),

* $p \leq .05$ (not significant after multiple comparison adjustment)

Table 5

Receiver operating characteristic curve using ECog total score by informant-report and self-report

	Informant report		Self-report		RAVLT Learning		HV		CSF Aβ 1–42	
Diagnostic group comparisons	***n***	**AUC**	***n***	**AUC**	***n***	**AUC**	***n***	**AUC**	***n***	**AUC**
1 AD vs Normal	511	.99 (CI = .98−.99)	519	.79 (CI = .74−.83)	516	.97 (CI=.96−.98)	325	.89 (CI=.86−.93)	183	.84 (CI=.78−.90)
2 LMCI vs Normal	549	.88 (CI = .85−.91)	558	.80 (CI = .77−.84)	555	.80 (CI=.76−.84)	362	.72 (CI=.67−.77)	191	.73 (CI=.65−.80)
3 EMCI vs Normal	605	.83 (CI = .80.−86)	617	.79 (CI = .75.−82)	615	.67 (CI=.62.−71)	503	.54 (CI=.49.−59)	187	.63 (CI=.55.−71)
4 “Impaired” vs Normal	1065	.89 (CI = .87.−91)	1080	.79 (CI = .76.−82)	1074	.79 (CI=.76.−82)	800	.67 (CI=.63.−71)	401	.73 (CI=.67.−80)
5 AD vs EMCI	516	.90 (CI = .88.−93)	522	.53 (CI = .48.−58)	519	.92 (CI=.90.−94)	438	.85 (CI=.82.−89)	210	.74 (CI=.67.−80)
6 LMCI vs EMCI	554	.62 (CI = .57.−66)	561	.51 (CI = .46.−56)	558	.67 (CI=.62.−71)	475	.68 (CI=.63.−73)	218	.59 (CI=.51.−66)
7 AD vs LMCI	460	.84 (CI = .80.−88)	463	.52 (CI = .46.−57)	459	.82 (CI=.78.−86)	297	.71 (CI=.65.−77)	214	.68 (CI=.61.−75)

Note: Impaired = AD + EMCI + LMCI groups; AUC=area under the curve; 95% CI=confidence interval; ECog=Everyday Cognition score; RAVLT=Rey Auditory Verbal Learning Test; HV=hippocampal volume; CSF=cerebrospinal fluid