Published in final edited form as:
Alzheimers Dement. 2014 January ; 10(1): . doi:10.1016/j.jalz.2013.01.003.

Subjective Cognitive Decline: Self and Informant Comparisons

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Abstract

Background—It is unclear whether self or informant-based subjective cognition better distinguishes emotional factors from early stage Alzheimer's disease (AD).

Methods—447 healthy members of the Arizona Apolipoprotein E (APOE) Cohort and their informants completed both the self and informant paired Multidimensional Assessment of Neurodegenerative Symptoms questionnaire (MANS).

Results—30.6% of members and 26.2% of informants endorsed decline on the MANS. Both self and informant-based decliners had higher scores of psychological distress and slightly lower cognitive scores than nondecliners. Over the next 6.7 years, 20 developed mild cognitive impairment (MCI). Converters were older at entry than nonconverters (63.8[7.0] vs 58.8[7.3] years, p=.003), 85% were APOE e4 carriers (p<.0001), and they self-endorsed decline earlier than informants (58.9[39.2] vs 28.0[40.4] months before MCI; p=.002).

Conclusions—Both self and informant based subjective decline correlated with greater psychological distress, and slightly lower cognitive performance. Those with incident MCI generally self-endorsed decline earlier than informants.

1. Introduction

Subjective cognitive complaints are common, but their clinical significance is not always clear. Stage two of the 1982 Global Deterioration Scale for Primary Degenerative Dementia defines "very mild cognitive decline" as a disease phase in which patients complain of memory loss but have no clinical, psychometric, or functional evidence of decline (1,2). Nonetheless, whether subjective memory complaints represent early stage Alzheimer's disease (AD) or not has remained highly controversial. Clinical (3) as well as large population-based cross sectional (4) and longitudinal (5) studies have found memory complaints to correlate more closely with psychological factors such as anxiety and depression than with psychometrically objective impairment. More recently, however, a longitudinal study of 2415 German primary care patients age 75 years and older reported

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greater rates of incident mild cognitive impairment (MCI) and AD at one and three years of followup among those expressing concern about their memory (6). Reisberg et al reported similar results in a cohort of 213 cognitively normal individuals followed for at least 7 years although the baseline characteristics of those with subjective memory complaints revealed them to be older and with lower baseline cognitive performance compared to those without such complaints (7).

By the time individuals with subjective complaints reach a clinical setting, informant reports are often used to validate the patient's concern, but in the setting of minimal to no objective patient impairment, it is unclear whether the patient or the informant is able to provide the more medically salient history. We therefore sought to compare the responses of individuals and their informants on the Multidimensional Assessment of Neurodegenerative Symptoms questionnaires (MANS) (8), paired self and informant based questionnaires sensitive to the cognitive, behavioral, and movement related problems that are prevalent among patients with early stage AD and related disorders.

2. Methods

2.1 Study participants and enrollment

Cognitively normal residents of Maricopa County age 45–79 years with a family history of dementia were recruited through local media ads into the Arizona APOE cohort, a longitudinal study of cognitive aging (9). Demographic, family, and medical history data were obtained on each individual undergoing APOE genotyping, and identity was coded by a study assistant. All individuals gave their written, informed consent, approved by the Institutional Review Boards of Mayo Clinic and Banner Alzheimer Institute, and agreed to have the results of the APOE test withheld from them as a precondition for their participation in this study. Genetic determination of APOE allelic status was performed using a polymerase chain reaction (PCR) based assay (10).

Screening tests included a medical history, neurologic examination, the Folstein Mini-Mental Status Exam (MMSE; 11), the Hamilton Depression Rating Scale (Ham-D; 12), the Functional Activities Questionnaire (FAQ), Instrumental Activities of Daily Living (IADL), and Structured Psychiatric Interview (13). There were no potentially confounding medical, neurological, or psychiatric problems (such as prior stroke, traumatic brain injury, memory or other form of cognitive impairment, parkinsonism, major depression, or substance abuse). None met the published criteria for MCI (14), AD (15), or any other form of dementia (13), or major depressive disorder (13). On the MMSE, participants had to score at least 27 based on published age and education-based norms (and must have scored at least 1 out of 3 on the recall subtest) (11). On the Ham-D, participants had to score 10 or less (12) at the time of their first visit. All FAQ and IADL questions had to indicate no loss of function.

2.2 Neuropsychological testing

Those fulfilling these requirements were administered an extensive standardized battery of neuropsychological tests that was repeated every two years. The neuropsychological tests within our battery are detailed in reference 16, and encompass four broadly defined cognitive domains. The scores used were as follows:

Memory—Auditory Verbal Learning Test Long Term Memory Score ([LTM], 30 minute delayed recall of a 15 word list, maximum possible is 15); Buschke Free and Cued Selective Reminding Test Total Free (SRT-free) Recall (maximum is 112), Rey-Osterrieth Complex Figure Test Absolute Recall (CFT-recall; maximum possible is 36); the Wechsler Memory

Scale-Revised Paragraph Recall (one story, total 30 minute delayed recall); and the Benton Visual Retention Test total number correct (VRT; maximum possible is 10).

Executive—Wisconsin Card Sorting Test Total Errors (WCST-errors; lower scores are better), Paced Auditory Serial Attention Task 3 and 2 second versions total correct (PASAT-3, PASAT-2; mental arithmetic tests in which problems are presented 3 and 2 seconds apart; maximum possible for each is 60); Controlled Oral Word Association Test total words (COWAT; word generation over one minute for each of three letters; no upper limit, higher is better); Category fluency task (total vegetables named in one minute); Trail Making Test parts A (easier) and B (more difficult) total time to connect the alternating numbers and letters; and Age Scaled Scores (a score of 10 is 50th percentile) of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) subtests including Digit Span (DigSp), Mental Arithmetic (WAIS-arithmetic), and Digit Symbol Substitution Age Scaled Score (DSS).

Language—Boston Naming Test (BNT; 60 item), and Token Test total correct (maximum is 44).

Visuospatial—Judgment of Line Orientation total correct (JLO; maximum is 30), Facial Recognition Test Short Form corrected long form score (FRT; 27 matches), WAIS-R Block Design Age Scaled Score (BD), and the CFT copy score (maximum score is 36).

2.3 Behavioral Testing

As noted above, the Ham-D is an examiner-based depression measure (12) used to screen out those with potentially clinically significant depression. Participants also complete the Beck Depression Inventory (17), a generally applicable self-scored depression measure, and Geriatric Depression Scale (18), most appropriate for older age groups. Finally, participants completed the Personality Assessment Inventory (19) which surveys a wide variety of behavioral domains including somatization and anxiety in addition to depression (scores are reported as T-scores).

2.4 Subjective cognitive assessment

All participants and their informants (typically a spouse) completed the paired the Multidimensional Assessment of Neurodegenerative Symptoms questionnaires (MANS) (9). The MANS are paired self and informant based questionnaires comprised of 87 questions that assess changes over the preceding year in daily habits, personality, and motor functioning. It employs a quantitative scale for rating the frequency of a symptom from zero (never) to four (routinely), with intermediate values of one (once), two (occasionally), and three (more than monthly); scores can range from 0–348 with higher scores indicating more frequent and severe symptoms. Any score greater than zero was considered “positive” for endorsed decline on both the MANS-self and MANS-informant questionnaire.

2.5 Statistical analysis

Statistical analyses were performed using computer software SPSS (IBM). Categorical variables (sex ratio and APOE genotype) were examined using the Fisher-exact test, group differences on continuous measures were examined using parametric two-sample independent t-tests, or Mann-Whitney U tests for data that were not normally distributed, defined by MANS-self or MANS-informant being equal to, or greater than, zero. Conversion ratios between the MANS=0 and the MANS>0 groups were compared using chi square. Significance of p=0.05, two-tailed, was used for all analyses. Bonferroni correction was used to adjust for multiple comparisons separately within the behavioral and cognitive categories of results.

2.6 Clinical conversion

Participants were all normal at entry but those who subsequently developed symptomatic cognitive impairment underwent a standard clinical assessment that included a neurological examination with mental status testing, neuropsychological assessment (if not already completed within 6 months of the complaint), brain imaging (CT or MRI), and standard blood tests to exclude common mimics and potentially reversible causes. MCI was diagnosed according to the modified Petersen Criteria adopted by the American Academy of Neurology (14), and Alzheimer's disease according to 1984 NINCDS/ADRDA criteria (15).

3. Results

Of 2482 individuals who underwent APOE genotyping, 704 completed at least one epoch of neuropsychological testing. Of these, 588 completed the MANS-informant, 572 completed the MANS-self, and 447 completed both the self and informant versions of the MANS and so were included in this analysis. Demographic data are summarized in table 1. Mean age was 59.0 (7.4), education 15.6 (2.4) years, and MMSE score 29.6 (.7). 69% were women, and 40% were APOE e4 carriers. In the MANS-self analysis, there was no difference in age, gender, or e4 carrier proportion between those with scores of zero or greater than zero. In the MANS-informant analysis, however, those with MANS-informant scores greater than zero were older (p=.031), with a higher proportion of e4 carriers (p=.049, Fisher exact test), and less female predominance (p=.001, Fisher exact test). Family history of a first degree relative with dementia was present in 71.8% of the sample. This did not differ by MANS-self response (p=.64, Fisher exact test), but was slightly higher among those whose informant did not report decline (73.9 vs 63.4%, p=.04). 310 scored zero on the MANS-self (no change within the past year) and 137 scored above zero (indicative of some change within the past year). Of those scoring above zero, the mean score was 36.1 (32.4). For both self and informant responses, 85% related to cognitive concerns, 9% to behavioral, and 6% to movement. The most common self-endorsed concerns included losing/misplacing objects and forgetting names; informants reported misplacing/losing items, personality changes, and forgetting events and appointments.

Table 2 shows the results of the cognitive and behavioral tests in the MANS = 0 and MANS > 0 subgroups for both the self-rated and the informant-rated questionnaires. Although all scores are well within normal limits (and many in the superior range), those whose MANS-self scores were greater than zero performed slightly but significantly less well on the MMSE, VRT, WAIS-arithmetic, WCST-errors, and CFT-copy, but after Bonferroni correction, only the MMSE and WAIS-R mental arithmetic differences remained significant. Those whose MANS-informant scores were greater than zero performed less well on CFT-recall, logical memory, WCST-errors, and CFT-copy, but after Bonferrini correction only the CFT recall difference remained significant. Table 2 also shows the results of the behavioral measures. Again, all scores were well within normal ranges. Nonetheless, all four of the four depression measures (Ham-D, Beck, GDS, and PAI-Depression) were significantly higher in the Self > 0 subgroup as were measures of anxiety (PAI-Anxiety), stress (PAI-Stress), and somatization (PAI-Somatization), and all remained significant after Bonferroni correction. Informant based differences were nearly identical on the behavioral measures, and all except the Ham-D and PAI-SOM remained significant after Bonferroni correction.

Overall followup duration for the cohort was 80.8 (57.4) months over which time, 20 members subsequently met criteria for MCI (mean age at conversion 71.5 [6.6] years). For the MANS-self, 6.9% of those endorsing decline converted while 2.6% of those not endorsing decline did so (O.R. 2.78, p<.05). Similarly, for the MANS-informant, conversion rates for those endorsing or not endorsing decline were 9.4% and 2.2% respectively (O.R.

4.58, p<.05). Those who developed MCI were older at entry than nonconverters (63.8 [7.0] vs 58.8 [7.3] years, p=.003), with a higher proportion of APOE e4 carriers 85% vs 38.2%, p<.0001, Fisher's exact test) and male gender (55% vs 30%, p=.03, Fisher's exact test), and they performed less well on multiple memory measures (table 3). Entry MANS-self scores, but not informant scores were slightly higher in MCI converters (p=.034). Self endorsement of decline preceded informant in 11, coincided in eight, and trailed in one. Overall members self-endorsed decline earlier than their informants (58.9[39.2] vs 28.0[40.4] months before MCI; p=.002).

4. Discussion

In our cohort overall, we found that both self and informant-reported decline correlated with greater psychological distress and mildly lower cognitive performance. Incident MCI converters, however, had higher MANS-self (but not informant) scores and performed worse than nonconverters on memory measures at entry, but not on behavioral measures. These results are generally consistent with previous research. We were also able to compare self and informant endorsed decline showing that both correlated with psychological measures of stress. Self-rated decline on average preceded informant-rated decline among those who developed MCI, but informant rated decline seemed more highly predictive of subsequent conversion in our small sample of converters.

The association of self reported cognitive decline with psychological distress, especially depression, anxiety, and somatization (3–5), has led many to question the clinical relevance of subjective cognition to AD or other neurodegenerative dementias. However, evidence supporting its biological validity is accruing. Several recent cohort studies have shown that subjective decline implies an increased risk of subsequent clinical conversion (6,7), but not all (20). While MRI studies of individuals with subjective memory loss have yielded mixed results (4,21) a recent PiB-PET study compared cognitively normal older adults with higher and lower measurements of cerebral amyloid deposition. Those with more amyloid deposition had the subjective impression of lower memory performance, as well as lower memory scores (22).

In addition to having higher scores on measures of psychological distress, those endorsing subjective decline had slightly but significantly lower scores on some cognitive measures. Informant-based impressions of decline correlated with a similar pattern. In prior studies, declarative memory measures (such as word list retention) have proven to be sensitive to preclinical decline (9), while mental arithmetic tests also declined but much less robustly than memory (23).

The following limitations should be kept in mind when considering the results of our study. First, our results represent those of a group, and despite a small subset with incident MCI, most of those endorsing subjective decline did not develop evidence of objective decline or receive a clinical diagnosis over an average of more than six years of followup. Therefore, one should not infer that everyone with subjective memory complaints necessarily has preclinical AD. Second, because our cohort contains a high proportion of APOE e4 carriers subjective complaints were more likely to indicate early stage AD than would be true in a community-based cohort. On the other hand, ours is also a relatively young cohort and it is possible that subjective decline may have greater significance in older individuals. Finally, the relative lack of correlation between informant-reported decline and incident MCI in this study does not imply that informants are unreliable. Our incident MCI subset was small, and in roughly half the cases, informant reports correlated with subjective reports. Rather, our data suggest that individuals can become self-aware of change before observers detect any

signs of decline. Further comparison of self-and informant reports in a larger incident MCI cohort is needed to address this question further.

In summary, subjective decline, whether self or informant-based, can be an early harbinger of objective cognitive decline, but its association with psychological distress makes it clinically challenging to interpret.

Acknowledgments

Funding support from NIA R01AG031581, NIA P30AG19610, and the Arizona Alzheimer's Consortium. The authors wish to thank Bruce Henslin, Sandra Yee-Benedetto, Travis Johnson, Marci Zomok, Jessie Jacobsen, Jeanne Young, Jennifer Pichon, Lynn Autry, Allyson Jensen, and Andrea Fowler for expert technical support.

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Research in Context

Systematic Review. We searched PubMed with the terms “subjective cognition,” “preclinical Alzheimer’s disease”, “cognitive aging”, “age associated memory impairment”, “mild cognitive impairment”, “apolipoprotein E and cognition” and “global deterioration scale” and searched for studies correlating subjective cognitive concerns in neuropsychologically unimpaired individuals with psychological and cognitive outcomes. We identified several clinical[3–7], neuropsychology[1–7] and imaging biomarker[17,18] studies of particular relevance.

Interpretation. The results of our study show that there is considerable overlap between self and informant based subjective decline and that both correlate not only with measures of psychological distress but also with cognitive measures sensitive to emotionally sensitive executive skills. We also were able, for the first time, to correlate both self and informant reports with clinical outcomes and found that self-reported decline preceded informant-observed decline in roughly half our case and coincided in the other half (with informant reported decline preceding self-reported decline in only a single case). Our findings support both sides of the current argument that subjective decline is indeed highly correlated with psychological distress but that it also seems to contain a clinically relevant signal in some cases making it a potential sign of preclinical Alzheimer’s disease/impending MCI.

Future Directions. Continued followup of our cohort with a larger number of incident MCI and dementia cases, as well as further correlation with AD biomarkers will allow us to better identify those factors that most reliably distinguish a true “biological signal” from “psychological noise” among patients with subjective cognitive complaints in the absence of objective cognitive impairment.

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Table 1

Demographics

	Self = 0	Self > 0	p*	Informant = 0	Informant > 0	p*
N	310	137		330	117	
Age	58.7 (6.9)	59.8 (8.3)	0.15	58.6 (7.0)	60.3 (8.3)	0.031
Education	15.7 (2.4)	15.5 (2.6)	0.6	15.7 (2.4)	15.4 (2.5)	0.16
Female (%)	219 (70.8%)	93 (68.1%)	0.58	242 (73.3%)	66 (56.4%)	0.0011
APOE e4+ (%)	136 (43.8%)	53 (38.4%)	0.3	123 (37.3%)	56 (47.9%)	0.049
MMSE	29.7 (.6)	29.4 (.8)	<.0001	29.6 (.7)	29.6 (.7)	0.24
MANS-Self	0	36.1 (32.4)	<.0001	6.3 (17.1)	24.6 (35.0)	<.0001
MANS-Informant	4.7 (13.0)	15.0 (28.0)	<.0001	0	30.0 (28.1)	<.0001

* unpaired t-tests used to compare groups for continuous data (except for the MMSE, Mann-Whitney U-test) and Fisher's exact test for categorical data. All p values are two-tailed.

APOE=Apolipoprotein E; MMSE=Mini-mental Status Exam; MANS=Multidimensional Assessment of Neurodegenerative Symptoms

Table 2

Psychometric Data

	Self = 0	Self > 0	p*	Informant = 0	Informant > 0	p*
Behavioral Data						
Hamilton Depression Scale	1.9 (2.6)	3.4 (3.7)	<.0001	2.1 (2.8)	2.9 (3.5)	0.007
Beck Depression Inventory	3.1 (3.3)	6.3 (5.1)	<.0001	3.7 (4.0)	5.2 (4.6)	0.0004
Geriatric Depression Scale	2.1 (2.6)	4.4 (4.7)	<.0001	2.3 (3.0)	4.0 (4.5)	<.0001
PAI-Somatization	45.8 (5.7)	49.7 (9.6)	<.0001	46.5 (6.7)	48.4 (8.6)	0.04
PAI-Anxiety	44.5 (5.7)	47.2 (7.4)	.0002	44.8 (6.0)	46.7 (7.1)	0.008
PAI-Depression	45.0 (6.7)	48.6 (8.7)	<.0001	45.4 (7.4)	48.4 (7.7)	<.0001
PAI-Stress	43.4 (6.2)	46.5 (9.4)	<.0001	43.4 (6.2)	46.5 (10.0)	0.0006
Cognitive Data						
MMSE	29.7 (.6)	29.4 (.8)	<.0001	29.6 (.7)	29.6 (.7)	0.24
AVLT-LTM	9.2 (3.4)	9.2 (3.0)	0.97	9.4 (3.4)	8.7 (3.0)	0.063
SRT-total free	87.1 (11.9)	87.8 (10.9)	0.72	87.8 (11.7)	85.8 (11.2)	0.09
CFT-recall	18.2 (6.6)	17.7 (5.8)	0.43	18.6 (6.4)	16.5 (6.1)	0.0018
Visual Retention Test	6.9 (1.9)	6.5 (1.9)	0.03	6.9 (1.9)	6.5 (2.0)	0.1
WMS logical memory delay	12.7 (4.0)	12.0 (3.8)	0.13	12.9 (3.8)	11.6 (4.2)	0.0091
COWA	45.7 (11.1)	44.6 (10.2)	0.46	45.9 (10.8)	43.8 (10.8)	0.06
Categories-vegetables	15.5 (4.3)	14.9 (4.3)	0.17	15.5 (4.1)	14.9 (4.9)	0.09
PASAT-3 second	45.8 (11.9)	42.9 (13.8)	0.054	45.6 (12.2)	43.0 (13.2)	0.059
PASAT-2 second	34.3 (11.4)	32.1 (12.2)	0.066	33.8 (11.9)	33.2 (11.0)	0.69
WAIS-arithmetic	11.9 (2.5)	10.9 (2.7)	0.0002	11.7 (2.6)	11.3 (2.7)	0.09
WAIS-digit span	11.3 (2.8)	10.5 (2.6)	0.005	11.3 (2.7)	10.7 (2.8)	0.17
WAIS-DSS	12.6 (2.1)	12.4 (2.2)	0.57	12.7 (2.0)	12.2 (2.2)	0.14
WCST-errors	29.3 (19.5)	33.2 (19.6)	0.015	29.4 (19.1)	33.6 (20.7)	0.045
TMT-A seconds	28.0 (9.0)	29.2 (10.6)	0.54	27.9 (9.5)	29.6 (9.5)	0.051
TMT-B seconds	71.0 (27.9)	76.7 (36.6)	0.38	71.2 (28.8)	76.7 (35.3)	0.27
Boston Naming Test	56.2 (3.5)	55.9 (3.1)	0.075	56.3 (3.3)	55.6 (3.7)	0.078
Token	42.9 (2.0)	42.6 (2.1)	0.071	42.9 (1.9)	42.7 (2.3)	0.44

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	Self = 0	Self > 0	p*	Informant = 0	Informant > 0	p*
Judgment of Line Orientation	24.9 (3.6)	24.7 (3.8)	0.79	24.8 (3.7)	25.0 (3.7)	0.47
Facial Recognition Test	46.7 (4.0)	46.3 (3.5)	0.15	46.6 (3.8)	46.4 (3.8)	0.57
CFT-copy	34.4 (2.4)	34.1 (2.5)	0.026	34.5 (2.3)	33.8 (2.7)	0.008
WAIS-Block Design	12.1 (2.6)	11.8 (2.3)	0.33	12.0 (2.5)	12.0 (2.4)	0.91

*Mann-Whitney U tests used to compare groups for continuous data. All p values are two-tailed.

PAI=Personality Assessment Inventory, MMSE=mini-mental state exam, AVLT-LTM=Auditory Verbal Learning Test-Long Term Memory, SRT=Selective Reminding Test, CFT=Complex Figure Test, WMS=Wechsler Memory Scale (revised), COWA=Controlled Oral Word Association Test, PASAT=Paced Auditory Serial Attention Task, WAIS=Wechsler Adult Intelligence Scale (revised), DSS=Digit Symbol Substitution, WCST=Wisconsin Card Sorting Task, TMT=Trail Making Test

Table 3

Incident Mild Cognitive Impairment

	Incident MCI (Entry Data)	Nonconverters (Entry Data)	p*
Demographics			
N	20	427	
Age	63.8 (7.0)	58.8 (7.3)	0.003
Education years	15.4 (1.7)	15.6 (2.4)	0.67
Female (%)	9 (45%)	299 (70%)	0.03
APOE e4 carriers (%)	17 (85%)	163 (38.2%)	<0.0001
MANS-Self	21.8 (34.9)	10.7 (24.0)	0.034
MANS-Informant	15.9 (33.1)	7.5 (18.8)	0.39
Behavioral Data			
Hamilton Depression Scale	3.0 (3.4)	2.3 (3.0)	0.36
Beck Depression Inventory	3.8 (3.5)	4.1 (4.2)	0.95
Geriatric Depression Scale	4.9 (4.0)	2.7 (3.5)	0.0079
PAI-Somatization	46.5 (5.7)	47.0 (7.4)	0.95
PAI-Anxiety	45.3 (5.8)	45.3 (6.4)	0.94
PAI-Depression	46.1 (6.5)	46.1 (7.6)	0.43
PAI-Stress	45.9 (6.2)	44.3 (7.6)	0.14
Cognitive Data			
MMSE	29.4 (.8)	29.6 (.7)	0.14
AVLT-LTM	6.8 (2.6)	9.3 (3.3)	0.0007
SRT-total free	77.7 (12.6)	87.7 (11.3)	0.0005
CFT-recall	16.0 (5.9)	18.1 (6.4)	0.11
Visual Retention Test	5.5 (1.9)	6.9 (1.9)	0.002
WMS logical memory delay	8.2 (5.0)	12.7 (3.8)	.0003
COWA	43.5 (9.1)	45.4 (10.9)	0.56
Categories-vegetables	10.8 (3.4)	15.5 (4.2)	<.0001
PASAT-3 second	39.5 (18.4)	45.2 (12.1)	0.19
PASAT-2 second	30.1 (15.5)	33.8 (11.5)	0.51
WAIS-arithmetic	11.8 (2.4)	11.6 (2.6)	0.67
WAIS-digit span	11.9 (2.5)	11.0 (2.8)	0.14
WAIS-DSS	12.0 (2.0)	12.6 (2.1)	0.22
WCST-errors	36.6 (19.2)	30.2 (19.6)	0.1
TMT-A seconds	34.3 (10.5)	28.1 (9.4)	0.012
TMT-B seconds	107.4 (47.8)	71.2 (28.9)	.0013
Boston Naming Test	55.7 (3.6)	56.1 (3.4)	0.65
Token	43.2 (1.5)	42.8 (2.0)	0.69
Judgment of Line Orientation	24.7 (3.5)	24.8 (3.7)	0.8
Facial Recognition Test	44.6 (3.5))	46.6 (3.8)	0.017
CFT-copy	32.7 (4.1)	34.4 (2.3)	0.063
WAIS-Block Design	11.7 (2.2)	12.0 (2.5)	0.52

* unpaired t-tests used to compare groups for continuous demographic data and Mann-Whitney U tests for neuropsychological and behavioral data; Fisher's exact test was used for categorical data. All p values are two-tailed.

PAI=Personality Assessment Inventory, MMSE=mini-mental state exam, AVLT-LTM=Auditory Verbal Learning Test-Long Term Memory, SRT=Selective Reminding Test, CFT=Complex Figure Test, WMS=Wechsler Memory Scale (revised), COWA=Controlled Oral Word Association Test, PASAT=Paced Auditory Serial Attention Task, WAIS=Wechsler Adult Intelligence Scale (revised), DSS=Digit Symbol Substitution, WCST=Wisconsin Card Sorting Task, TMT=Trail Making Test