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The Cognitive Change in Women Study (CCW): Informant Ratings of Cognitive Change but not Self Ratings are Associated with Neuropsychological Performance Over Three Years

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Abstract

The value of self-reported memory complaints for identifying or predicting future cognitive decline or dementia is controversial, but observations from a third party, or "informant", may prove more useful. The relationship between Informant and Self ratings of cognitive status and neuropsychological test scores was examined in a cohort of 384 non-demented, community-dwelling women, aged sixty and older, participating in a single-site Women's Health Initiative ancillary study. Each participant and her respective informant separately completed the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[1]. Participants also underwent neuropsychological testing and responded to questionnaires on depression and functioning in complex activities of daily living. All neuropsychological test scores were significantly correlated (p-values <.05 to <.01) with Informant IQCODE ratings while Self ratings overestimated cognitive functioning in some domains. Furthermore, the Self and Informant ratings were both positively correlated with depression and negatively correlated with participants' activity level. Therefore, Informant judgments of functional abilities are robust predictors of cognitive status in high functioning non-demented women. These results suggest that informants may be sensitive to changes that are not clinically significant but that may represent an incipient trend for decline.

Keywords

Normal Aging; IQCODE; Informant-rating; Self-rating; Cognitive impairment; Screening

The cognitive changes that "normally" accompany aging are often simply an annoyance to the individuals who experience them, but, in some instances these changes may herald a

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more perilous course of decline to a state of dementia. Many older individuals complain about memory changes, but whether or not subjective memory complaints are valid for identifying or predicting dementia is debatable. Some studies have shown that subjective memory complaints predict future dementia[2–3], while others have found that subjective complaints do not predict cognitive decline[4–5].

Subjective complaints may lack validity because they can be influenced by personality traits[6] or emotional status at the time of the complaints[7]. However, recent studies using structural neuroimaging found that subjective complaints may have biological relevance. For example, in one study individuals with subjective complaints had smaller hippocampal volumes than those with no such complaints[8–9]. In another study, a greater proportion of individuals who possessed an e4 allele of the gene for Apolipoprotein E (APO E4), a genetic risk factor for Alzheimer's disease (AD), had more subjective complaints than those without this allele[10–11]. Thus, it is worthwhile to study the meaning of subjective complaints in individuals who are aging and at risk for AD.

Although the utility of subjective complaints for predicting cognitive decline is controversial, there is more evidence supporting the use of third party or "informant" reports, for this purpose. Tierney et al.[12] found that informant perceptions of cognitive deficits contributed significantly to the prediction of AD, whereas subjective perceptions did not. The diagnosis of dementia requires the presence of alterations in daily living activities[13]. One of the most widely used and pathologically validated instruments to stage preclinical and subsequent stages of Alzheimer's disease, the Clinical Dementia Rating scale[14], is based heavily on informant report. The AD8[15] is another informant based questionnaire that is brief and can reliably differentiate between nondemented and demented individuals. Thus, informant reports may have several advantages over neuropsychological testing for the detection of dementia because informant reports typically have more everyday relevance to functional capacity and also have a longitudinal perspective.

Jorm and colleagues developed and validated an informant questionnaire to screen for dementia, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE[1,5]). The IQCODE is designed to capture an informant's opinion as to whether the participant has improved, stayed the same, or declined over the last ten years in a series of functional situations that emphasize cognitive ability (e.g. remembering things that have happened recently, recalling conversations a few days later). The IQCODE has high internal reliability (alpha=0.95) and high test-retest reliability over a one-year period (r=0.75)[16]. Using a cut point of ≥3.30 Jorm[17] reported sensitivity of 79% and specificity of 83%. A shortened version of the IQCODE consists of 16 items and has sensitivity of 79% and specificity of 82% for a diagnosis of dementia using a cut point of ≥3.38[17].

Jorm and colleagues[18] have shown that the IQCODE score significantly correlates with scores on the Mini-Mental State Examination (MMSE), tests of episodic memory, and tests of mental processing speed. Other studies also have shown a correlation between IQCODE and MMSE scores[19–20]. More recently, Isella and colleagues[21] showed that the IQCODE can contribute to the diagnostic and prognostic investigation of patients with "mild cognitive impairment" (MCI), a condition that may constitute a risk factor for AD[22]. Finally, researchers have found that the IQCODE in patients with dementia[23–24] and mild cognitive impairment[21] yields a more reliable diagnosis than sole reliance on objective neuropsychological test scores.

To date, studies using the IQCODE have focused on populations with dementia or mild cognitive impairment. There has been a trend in research on cognitive aging to pursue the very earliest signs, prior to MCI that might signal future decline. Thus, the utility of the

IQCODE for predicting cognitive decline in cognitively normal older individuals warrants further exploration. Furthermore, the IQCODE might offer another perspective on cognitive decline by quantifying *self* rather than informant observations. That is, the IQCODE could be administered to individuals asking them to consider their own level of functional ability and whether or not there have been changes over the past 10 years. Such an adaptation of the IQCODE might be valuable to determine the validity of self-ratings. Jansen[25] found that the IQCODE when administered as a self-report measure meets the basic requirements of a good measurement in that it shows acceptable feasibility, good homogeneity, and construct validity. However, this study did not compare self and informant ratings for their ability to identify individuals at risk for dementia. Informants are not always available and, if it turns out that self-ratings are reliable, then these could substitute for the absent informant. Alternatively self ratings may not be valid.

The current study investigated whether or not the IQCODE is a valid measure of subjective reports of cognitive function in persons with psychometrically normal cognitive aging and to determine whether informant-rating or self-rating is more predictive of objective neuropsychological test scores. This study was carried out in a cohort of non-demented women over age 60 studied over a three-year interval in the Cognitive Change in Women (CCW) project. The CCW is a single site ancillary study to the Women's Health Initiative (WHI). The main goal of the CCW is to examine effects of nutritional and lifestyle factors on cognitive function in women age 60 and over. The CCW study employed an extensive battery of neuropsychological tests in multiple cognitive and behavioral domains, increasing the likelihood of identifying early indicators of cognitive loss.

Methods

Participants

Participants in this study were women enrolled in the Cognitive Change in Women (CCW) study. The design and methods of the CCW study are described in detail elsewhere[26]. The institutional review boards of Northwestern University, Evanston Northwestern Healthcare, and New England Research Institutes approved the study, and all participants signed informed consent forms. In brief, 554 non-demented, community dwelling women age 60 and over were recruited from the Women's Health Initiative (WHI) Observational Study and from the control ("usual diet") group of the WHI Diet Modification arm at Northwestern University. Thus, none of the women enrolled in the CCW ancillary study were receiving any type of treatment or intervention through the WHI. Methods for recruitment to the WHI study, and descriptions of the study arms from which our subjects were recruited are described in detail elsewhere[24].

The original WHI inclusion criteria required that women be post-menopausal. For the CCW study, in addition to age 60 and over, inclusion criteria entailed the following: 1) no history of Alzheimer's disease, other dementia, stroke, traumatic brain injury, and other neurologic disease (such as Parkinson's, epilepsy, etc.); 2) no history of chronic mental illness or mental illness requiring hospitalization; 3) no history of alcohol or substance abuse; 4) no current use of neuroleptics or long-term use of other major psychoactive medications; and 5) visual and hearing acuity (with or without correction) sufficient for valid neuropsychological testing, as determined in a screening interview. Individuals taking antidepressants related to situational stress were not excluded.

Participation in the CCW study entailed two visits, three years apart. At each visit, detailed demographic and health history information were obtained and neuropsychological tests were administered. Each participant was requested to have an informant ("study partner") who knew them for at least 10 years. The participants and their informants were

administered the IQCODE at both visits. Of the 544 women initially enrolled in the CCW study, 384 participants had complete IQCODE forms for themselves and an informant at their 3–year final visit. Data were not available for the remaining 160 participants for the following reasons: 64 participants did not return for the final visit (12% attrition); 28 participants' informants could not be contacted to complete the IQCODE despite multiple attempts; 39 participants could not provide an informant; and 29 participants were initial recruits to the study at a time when the IQCODE was not part of the protocol. There was no significant difference between the mean age at the baseline visit of those included in the analysis (M = 70.37 years, SD = 6.60), and those excluded (M = 71.38 years, SD = 5.99). Although there was a significant difference in education level of the participants included in the analysis 15.61 years (SD = 2.59) and excluded from the analysis 15.06 years (SD= 2.62) ($p < .05$), the magnitude of the difference was small. Furthermore, there was a significant difference between baseline cognitive function of the participants that were included in the analysis (Z = .07, SD = .50) and those excluded from the analysis (Z = −.19, SD = .67). Again, the magnitude of the difference was small. Participants included in the analysis were mostly Non-Hispanic, White (88%), and the remainder included African American (8%), Asian (2%), Hispanic (1%), and other (1%).

Procedure

At the initial CCW visit, each subject was interviewed to complete demographics, medical history, medication, and vitamin use forms. They were then administered neuropsychological tests and questionnaires. The informant/study partner was interviewed by telephone within the two weeks following the participant's appointment. If the informant was not reachable after three attempts over a two-week period, no further attempt was made to reach the informant. A final visit was completed three years later with identical procedures to the baseline visit.

Neuropsychological Measures

The neuropsychological tests (Table 1) had been selected to sample cognitive domains vulnerable to preclinical and early dementia of the Alzheimer type and to age-associated cognitive change. These tests were routinely used by the NIA-funded Northwestern University Alzheimer's Disease Center Clinical Core, to which the first 160 subjects for this study were recruited, funded by a pilot grant from the center. Memory was assessed with the Consortium to Establish a Registry for AD (CERAD) word list learning test[27–29] and the Logical Memory and Visual Reproduction subtests of the Wechsler Memory Scale-Revised (WMS-R)[30]. Executive function was assessed with two tests, Part B of Trail Making[31] and a short form of the Visual-Verbal Test[32]. Language was assessed with the Boston Naming Test[33], semantic fluency test (generating a list of animals for 60 seconds)[34], and a lexical fluency test (generation of lists of words with F, A, and S, each for 60 seconds)[35]. Attention was assessed using the Trail Making Test Part A[31] and WMS-R Digit Span Subtest[30]. Visual spatial function was assessed using the Judgment of Line Orientation (JLO)[36]. Last, as a global cognitive screen, the Mini Mental State Examination (MMSE)[37] was administered. In order to combine multiple test scores with different ranges into a composite score, a "global Z score" was created by combining the memory, executive function, language, attention and visual function neuropsychological scores into a summary score normalized to a mean of 0 and a standard deviation of 1.

In addition to neuropsychological tests, two self-report questionnaires were administered. The Geriatric Depression Scale[38] consists of thirty yes/no questions assessing self-reported symptoms of depression. A higher score indicates the participant endorsed more symptoms. The second questionnaire, the Adelaide Activity Profile (AAP)[39] samples complex activities

of daily living in healthy elderly by self-report. Higher AAP scores indicate higher self-reported activity levels by the participant.

The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)

The IQCODE was administered to the participant on the day of the baseline and final visits, following neuropsychological testing. The IQCODE consists of sixteen statements relating to memory and other cognitive functions. For each statement the participant was asked to rate on a scale of 1 (much better) to 5 (much worse) how much change she perceived in this skill or function over the last ten years. The total score was calculated by summing the response to each question then dividing by the total number of questions to yield an overall score between 1 and 5 (with higher scores indicating a reported decline in cognitive function). Informants were contacted within the next two weeks following the subjects' testing and the IQCODE was administered to the informant over the telephone. The informant was asked to rate the amount of the participant's decline or improvement for each of the sixteen items on the questionnaire over the same ten-year time interval.

Analyses and Statistical Methods

Two sets of analyses were undertaken. The first focused on relationships between the IQCODE ratings and the participant's current level of cognitive and psychosocial functioning by correlating the IQCODE ratings at the final visit with the neuropsychological scores, depression, and activity level at the *final visit*. Due to a more complete data set at the final visit, these data were used in the cross-sectional analysis rather than the initial visit data. The second set of analyses focused on the relationship between the IQCODE ratings and the participant's *change* in cognitive and psychosocial functioning over three years by correlating the IQCODE ratings at the final visit with the *change* in neuropsychological test scores, and with depression and activity level measures, between baseline and final visits. In this second analysis, the change score for each neuropsychological measure was calculated as the final visit score minus the baseline score.

Pearson correlations were used for these analyses to examine the linear relationships between the Informant and Self-ratings on the IQCODE and the neuropsychological tests, the Geriatric Depression Scale (GDS), and the Adelaide Activity Profile (AAP) and the change in neuropsychological test scores, depression score, and activity level score over a three-year period.

Results

Descriptive Statistics

The mean age of the participants at the initial visit was 70.37 years (SD= 6.60) and at the final visit was 73.33 years (SD= 6.60). As expected, in a community-dwelling sample of high-functioning women the average score on the IQCODE reflected a slight decline over a 10 year period for both self-rating (mean=3.08; SD=.31) and informant rating (mean=3.09; SD= .18). The median IQCODE score was 3.09 for self-rating and 3.06 for informant rating. The mode was 3.06 for the self-rating and 3.00 for informant rating. Although the measures of central tendency (mean, median, and mode) of the distributions of the self and informant ratings were very similar, the two distributions of scores correlated with neuropsychological data in strikingly different ways, as indicated below. The self-rating scores ranged from 1.00 to 4.19 (much better to somewhat worse) and the informant rating scores ranged from 2.50 to 4.19 (a little better to somewhat worse).

Correlations

Cross-Sectional Relationship between IQCODE and Final Visit Data—

Associations between neuropsychological tests scores, GDS, and activity level scores and Informant and Self IQCODE ratings at the final visit were examined. The Informant rating was significantly correlated with all of the neuropsychological tests at that point in time, including the global Z-Score, with negative correlation values ranging between −.39 and −.13 and positive correlation values ranging between .25 and .36 ($p < .01$ for all tests except digit span, $p < .05$), (Table 2). Thus, as a participant's score increased on the Informant rating (reflecting poorer function) their neuropsychological test scores declined. In addition, the Informant rating was positively correlated with the participant's GDS score ($p < .01$) and negatively correlated with the Adelaide Activity Profile ($p < .01$). Thus, as the informant reported more of a decline in the participant's cognition, the more the participant endorsed symptoms of depression and lower levels of activity. When using a post-hoc Bonferroni correction for multiple comparisons (with a family of 20 correlations and a *p* critical value of .0025), all measures were significantly correlated with the IQCODE except digit span.

In contrast, the Self-rating IQCODE score was significantly correlated with only four neuropsychological measures, the Visual Verbal Test sorts ($p < .01$), the Visual Verbal Test shifts, the MMSE, and Trail Making Test Part B ($p < .05$). However, the significant correlations for the Self-rating were not in the expected direction, i.e. there was a positive correlation with the Self-rating and MMSE score, Visual Verbal Test, and Visual Verbal shifts and a negative correlation with Self-rating and Trail Making Test Part B. Thus, participants who reported improvement over the last ten years were more likely to have lower scores on the neuropsychological tests. Furthermore, Self-rating scores significantly correlated with the GDS Score ($p < .01$) and AAP score ($p < .01$). As with the Informant rating, as participants reported more decline in their cognition, they endorsed more depressive symptoms and reported being less active. When using a post-hoc Bonferroni correction for multiple comparisons (with a family of 20 correlations and a *p* critical value of .0025), Visual Verbal Test shifts, the MMSE, and Trail Making Test Part B were no longer significantly correlated with the IQCODE.

Longitudinal Relationship between IQCODE and Change between Baseline and Final Visit Data—

Associations between the change in scores from baseline visit to final visit were examined for neuropsychological tests, GDS, activity level, and Informant and Self-ratings. The change in scores between baseline and final visits was an objective measure of any decline that may have occurred in the participant's cognitive ability over a three-year period.

The Informant rating significantly correlated with the difference in scores for several neuropsychological tests including CERAD word list trials ($p < .01$), CERAD word list recall ($p < .01$), Logical Memory immediate recall ($p < .01$), Logical Memory delayed recall ($p < .01$), MMSE ($p < .01$), Trail Making Test part A ($p < .01$), Trail Making Test part B ($p < .01$), Boston Naming Test ($p < .01$), and the Global Z-Score ($p < .01$), with negative correlation values ranging between −.31 and −.12 and positive correlation values ranging from .13 and .27 (Table 2). For all of the neuropsychological tests that showed a correlation with Informant ratings, a greater negative change between testing periods was associated with a higher IQCODE score at the final visit. Therefore, a greater decline in participants' cognition over the three-year period was associated with the informant endorsing decline over the last 10 years on the IQCODE. In addition, the Informant rating was negatively correlated with the change in total AAP score ($p < .05$). Furthermore, Informant rating was significantly correlated with change in GDS ($p < .05$). Therefore, for participants who reported more depressive symptoms at the final visit, informants were more likely to report a

decline in cognitive abilities during the final visit. When using a post-hoc Bonferroni correction for multiple comparisons (with a family of 20 correlations and a *p* critical value of .0025), the same measures were significantly correlated with the Informant IQCODE with the exception of the AAP and GDS. The Self-rating was not significantly correlated with any of the change scores for the neuropsychological tests, GDS, or AAP.

Discussion

The present study investigated the IQCODE in non-demented, community-dwelling, post menopausal women, aged 60 and older to determine if informant ratings were predictive of cognitive change over a three-year interval and if self ratings were also related to objective measures of change. The main findings of the study were that informants' ratings of cognitive change correlated with objective neuropsychological data. However, self reports using the IQCODE were not a valid estimation of cognitive functioning. In addition, both informant and self ratings of cognitive change were related to the participants' emotional status and activity level.

Participants' estimations of their own cognitive ability using the IQCODE did not correlate with objective cognitive test scores and in some cases over-estimated cognitive functioning. Therefore, the IQCODE is not a valid self-report measure of cognitive change in cognitively normal elderly. This is even more surprising given the fact that the participants completed the neuropsychological measures prior to completing the IQCODE. If giving the participants the IQCODE directly after the neuropsychological measures influenced their rating in any way it should have provided the participants with more awareness of their cognitive functioning, not less.

These results can be explained in several ways. First, as previously discussed, cognitive complaints may occur for reasons unrelated to actual cognitive decline, such as personality[6] and emotional status[7]. Our results show that objective neuropsychological scores did not correlate with self-ratings, but emotional status (depression) and activity level did. Second, participants who do notice cognitive change could be in denial (either implicitly or explicitly) and overcompensate by reporting improvement rather than decline over the ten year period. Lastly, many people with cognitive decline lack insight into their memory problems[40], resulting in a lack of complaints.

In contrast to the self ratings, informants' estimations of cognitive change using the IQCODE did correlate with participants' objective cognitive functioning. Therefore, these results support the previous findings that the IQCODE is a valid measure of cognitive function in the elderly when administered to an informant, and extend this finding to a non-demented cohort. In addition, informants' ratings of change correlated with the participants' depressive symptoms and activity level just as the participants' ratings themselves did. These findings should be taken into consideration when evaluating the results of the IQCODE because the results could be over-inflated due to emotional status and activity level.

Unlike the cross sectional data, not all of the longitudinal neuropsychological test data correlated with the IQCODE. This could be a function of the fact that the IQCODE inquires about a change over a ten-year period and the time course of the study was only three years.

Overall, our results are consistent with the findings of Jorm and others who reported that the IQCODE when filled out by an informant is a valid predictor of cognitive status and cognitive decline[18–20]. However, these findings have all been reported in patients with mild cognitive impairment or dementia[21, 23–24]. Therefore, our study shows that the IQCODE also can be utilized in a sample of community-dwelling women who are not demented and

still be a useful predictor of cognitive function and change over time. Although Jansen[25] found that the IQCODE when administered as a self-report meets the basic requirements of a good measurement, our results show that it is not a valid indicator of cognitive status or cognitive decline in this cohort of non-demented women. Therefore, when used in a research or clinical setting, the IQCODE is most informative when administered to informants, regardless of the cognitive status of the patient. Of note, the IQCODE was developed and validated in Australia [1, 16–17]. Therefore, this study provides information for its use in an American culture, which may have distinctive features.

There are some limitations to this study. First, it utilized a non-diverse sample mostly consisting of highly-educated Non-Hispanic White women. Further studies should be done examining the IQCODE in a more representative sample of gender, race/ethnic, and educational group. Second, because the IQCODE assesses change over a ten-year period, it would be ideal to follow participants over a ten-year period and assess their objective cognitive function in relationship to the IQCODE. Although there was a relationship between a three-year change in cognitive function and the IQCODE score, the relationship would most likely be stronger if the change was examined over a ten-year period; especially in cognitively-normal elders where changes may be very slight over a three year interval. Third, 160 women who were initially enrolled in the study were not included in the analysis because of the previously stated reasons. The baseline cognitive function and education of these women were significantly lower than the participants that were included in the analysis. Having a larger range of “normal” baseline cognitive function and education would have made the results stronger and more generalizable. Lastly, we did not record the informant’s relationship to the participant and how often the informant was in contact with the participant. However, if anything, controlling for this information could make the relationship between IQCODE and objective neuropsychological scores stronger.

Overall, we found that even in a high-functioning, non-demented sample of older women in a cognitive aging study, an informant is a better predictor of cognitive status than the participant. The trend in research on aging and cognitive function is to try to identify changes before they become clinically relevant[41–42]. This study supports the use of the informant-rated IQCODE as a “health check” measure in cognitively healthy older women and may identify those who are at higher risk for future dementia

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Table 1

Neuropsychological tests and self-report measures (and maximum scores).

DOMAIN	TESTS AND DERIVED SCORES
MEMORY	CERAD Word List[A] Trials 1–3 (30) Delayed Recall (10) WMS-R Logical Memory[A] Immediate Recall (50) Delayed Recall (50) WMS-R Visual Reproduction[A] Immediate Recall (41) Delayed Recall (41)
EXECUTIVE FUNCTIONS	Trail Making Tests[B] Part B, Time Visual Verbal Test[A] (10-item) Sorts (20) Shifts (10)
LANGUAGE	Boston Naming Test[A] (60) Semantic Fluency[A] Animals (Total in 60 seconds) Lexical Fluency[A] FAS (Total in 60 seconds)
ATTENTION	Trail Making Tests[B] Part A, Time WMS-R Digit Span Subtest[A] Raw Score (28)
VISUAL FUNCTIONS	Judgment of Line Orientation[A] (15)
GLOBAL COGNITIVE SCREEN	Mini Mental State Exam[A] (30)
SELF-REPORT MEASIRES	
ACTIVITY LEVEL	Adelaide Activity Profile[A] (69)
DEPRESSION	Geriatric Depression Scale[B] (30)
COGNITIVE DECLINE	IQCODE[B] (5)

[A] higher scores are indicative of better performance.

[B] lower scores are indicative of better performance.

Table 2

Correlation of Self and Informant IQCODE with neuropsychological test scores, GDS, and activity profile.

	Final Visit Data			Change Between Visits Data		
	Self	**Informant**	**Observations***	**Self**	**Informant**	**Observations***
Word List Trials		−0.303	384		−0.185	384
Word List Recall		−0.255	384		−0.151	384
Logical Memory I		−0.255	384		−0.156	384
Logical Memory II		−0.299	384		−0.192	384
Visual Reproduction I		−0.240	382			381
Visual Reproduction II		−0.273	382			381
MMSE	0.127#	−0.245	384		−0.175	384
MMSE Orientation		−0.195	384			384
Visual Verbal	0.134	−0.202	369			349
Visual Verbal Shifts	0.117#	−0.217	369			349
Category Fluency		−0.192	384			384
FAS Test		−0.186	383			383
Digit Span		−0.127#	382			363
Trail Making Test A		0.278	381		0.270	359
Trail Making Test B	−0.111#	0.335	379		0.233	357
Judgment of Line Orientation		−0.165	379			378
Boston Naming Test		−0.250	384		−0.151	383
Global Z Score		−0.391	384		−0.310	384
Adelaide Activity Profile	−0.183	−0.154	383		−0.118#	380
Geriatric Depression Scale	0.228	0.248	384		0.127#	383

*Some participants did not complete all of the neuropsychological tests and questionnaires

All values are significantly correlated at p <.01 except # values, which are correlated at p < .05. Non-significant findings have been excluded.