Neuropsychological Correlates of the Alzheimer’s Questionnaire (AQ)

A thesis submitted to the University of Arizona College of Medicine Phoenix in partial fulfillment of the requirements for the Degree of Doctor of Medicine

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Class of 2017

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Abstract

Informant-based assessments of cognition and function are commonly used to differentiate individuals with amnestic mild cognitive impairment (aMCI) and Alzheimer’s disease (AD) from those who are cognitively normal (CN). However, determining the extent to which informant-based measures correlate to objective neuropsychological tests is important given the widespread use of neuropsychological tests in making clinical diagnoses of aMCI and AD. The aim of the current study is to determine how well the Alzheimer’s Questionnaire (AQ) correlates with objective neuropsychological tests. Results showed that the AQ correlated strongly with the Mini Mental State Exam ($r = -0.71$) and the Mattis Dementia Rating Scale-2 ($r = -0.72$), and moderate correlations were noted for the AQ with memory function (Rey Auditory Verbal Learning Test Delayed Recall, $r = -0.61$) and executive function (Trails B, $r = 0.53$). The AQ also correlated moderately with language function (Boston Naming Test 30-Item, $r = -0.44$), but showed a weak correlation with visuospatial function (Judgment of Line Orientation, $r = -0.28$). The AQ also correlates particularly well with cognitive screens, showing the strongest correlations with the MMSE ($r = -0.71$) and the DRS-2 ($r = -0.72$). The findings of this study suggest that the AQ correlates well with several neuropsychological tests, particularly those that assess the domains memory and executive function. These results lend further support to the validity of the AQ as a screening instrument for cognitive impairment as it correlates well with neuropsychological measures used to make clinical diagnoses of aMCI and AD.

Keywords: dementia, mild cognitive impairment, Alzheimer’s disease, neuropsychology
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Introduction

As the prevalence of Alzheimer’s disease continues to increase [1], so too does the need for a brief and accurate informant-based screening tool for the detection of Alzheimer’s Disease (AD) and amnestic mild cognitive impairment (aMCI). Informant-based questionnaires are commonly used in both clinical and research settings for the purpose of differentiating aMCI and AD individuals from those who are cognitively normal (CN) [2,3]. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) and AD8 have demonstrated good diagnostic accuracy for AD and have been found to correlate well with other conventional cognitive screening tests, such as the Mini Mental State Examination (MMSE) [4,5].

The Alzheimer’s Questionnaire (AQ) is a 21-item, informant-based assessment designed for ease of use in the clinical setting that has demonstrated high sensitivity and specificity for both aMCI and AD [6,7]. The concurrent validity of the AQ with other established measures of cognition was demonstrated by Malek-Ahmadi et al [8] who found that the AQ correlates strongly with the Clinical Dementia Rating (CDR) Sum of Boxes and moderately with the MMSE and Montreal Cognitive Assessment (MoCA).

Although the diagnostic accuracy and concurrent validity of the AQ have been established [6-8], the degree to which the AQ is associated with neuropsychological and cognitive screening tests has not been investigated. Since neuropsychological tests are utilized in making clinical diagnoses of aMCI and AD, determining the extent to which the AQ correlates with objective and specific measures of various cognitive domains is needed in order further validate its ability to detect cognitive changes associate with aMCI and AD. This study will determine the extent to which the AQ correlates with performance-based neuropsychological tests commonly used in clinical settings, as well as its correlation with other cognitive screening instruments.
Methods

Study Sample

Data from 300 individuals participating in the Banner Sun Health Research Institute (BSHRI) Brain and Body Donation Program were utilized for this study [9]. Participants in this program are recruited predominantly from the northwest region of the Phoenix, Arizona metropolitan area. Written informed consent, approved by the (BSHRI) Institutional Review Board, was obtained from all subjects. Each subject with aMCI or AD was matched on age, education, and sex to a CN individual, without replacement. When an exact match could not be found, a tolerance of ±2 years was used for age and education in order to obtain an approximate match.

Both single and multiple domain aMCI cases were categorized as aMCI. Amnestic MCI cases were diagnosed using Petersen criteria [10]. The AD cases met NINCDS-ADRDA criteria for a clinical diagnosis of probable or possible Alzheimer’s disease [11]. The CN cases were defined as having no limitations of activities of daily living by informant report and were within normal limits on neuropsychological testing.

Consensus diagnoses were made by the study physician and neuropsychologist based on neuropsychological testing results, neurological and physical exam findings, and interviews with the subject and an informant that assessed global cognition, functional status, and mood and behavioral status. The AQ was not utilized in making the consensus diagnoses.
Table 1. Clinical Group and Study Sample Demographic Characteristics

<table>
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<tr>
<th></th>
<th>CN</th>
<th>aMCI</th>
<th>AD</th>
<th>Total</th>
<th>p-value</th>
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<td>83</td>
<td>67</td>
<td>300</td>
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<td>14.18±2.58</td>
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<td>Gender (M/F)</td>
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<td>44/39</td>
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Mean±standard deviation
Instruments

Alzheimer’s Questionnaire (AQ) [7] – A 21-item, informant-based dementia screening assessment designed for ease of use in a primary care setting. AQ items are divided into the following five domains: Memory, Orientation, Functional Ability, Visuospatial Ability, and Language. Items are posed in a yes/no format with the count of ‘yes’ responses equaling the total AQ score (0-27). Six items known to be predictive of a clinical AD diagnosis are weighted more heavily and are worth two points each.

Mini Mental State Examination (MMSE) [12] – A brief, 30-point cognitive screening instrument that includes items measuring Orientation, Memory, Language, Attention, and Visuospatial functions.

Montreal Cognitive Assessment (MoCA) [13] – A brief, 30-point cognitive screening instrument that assesses cognitive domains including Attention and Concentration, Executive Functions, Memory, Language, Visuoconstructual Skills, Conceptual Thinking, Calculations, and Orientation.

Mattis Dementia Rating Scale-2 (DRS-2) [14] – A widely-utilized, structured assessment of cognitive function. The instrument has five subscales: Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory, with the subscales used to derive a total score. For this study, only the total score was used for the analyses.

Clock Drawing Test [15] – Individuals are given a blank sheet of paper and asked to draw the face of a clock and to set the time to ten past eleven. A 10-point scoring system [15] was used which is based on three components: Integrity of Clock Face (0 – 2 points), Presence and Sequencing of Numbers (0 – 4 points), Presence and Placement of Hands (0 – 4 points).

Rey Auditory Verbal Learning Test (AVLT) [16] – A list of 15 words is read aloud to the individual, after which they are asked to recall as many words as possible in any order, for a total of 5 repeated trials. After the fifth trial, a new, distractor, 15-word list is read aloud to the individual, from which they recall as many words as possible. They are asked to recall the words they remember from the initial list after the distractor list and once more after a 20 minute delay. AVLT Total is the sum of the number of correctly recalled words for Trials 1-5. AVLT Delayed Recall is the number of correct words recalled after a 20-minute delay.
Brief Visuospatial Memory Test-Revised (BVMT-R) [17] – A test of visuospatial memory in which subjects are presented with a page containing six unique designs for 10 seconds. After the 10-second presentation, subjects are asked to draw the shapes on a blank page. Three such 10-second learning trials are administered, and after a delay of 20 to 25 minutes, subjects are asked to draw the shapes again on a blank page. BVMT-R Total Score is the sum of points from the three learning trials while the BVMT-R Delayed Recall is the number of points from the delayed recall trial.

Trails A [18] – The individual is instructed to draw a line that connects circled numbers in consecutive order.

Trails B [18] – The individual is asked to draw a line that connects circled numbers and circled letters in consecutive order while alternating between numbers and letters (1 – A – 2 – B – 3 – C, etc).

Digit Span Forward [19] – Number sequences of increasing length are read aloud to the participant, after which the number series is repeated back to the examiner.

Digit Span Backward [19] – Number sequences are read aloud to the participant, after which the number series is repeated back to the examiner in reverse order.

Controlled Oral Word Association Test [20] – Individuals are given one minute to say out loud as many words as they can that begin with a specified letter.

Animal Fluency [20] – Individuals are given one minute to say out loud as many names of animals as they can.

Stroop Color/Word [21] – The individual is presented with 5 columns of the words “blue,” “red,” and “green” presented in random order. The words are printed in an ink that is incongruent with the actual word itself (e.g., the word “blue” is printed in red ink). The individual is then asked to identify the color of the ink of the printed word. There is a 45-second time limit in which the individual must give as many correct responses as possible.

Judgment of Line Orientation (JLO) [22] – Individuals are asked to match a set of two lines, set at varying angles and lengths, to their respective reference lines located below each stimulus card.
Block Design [23] – Subjects manipulate a set of colored blocks to create a design matching the stimulus design.

Boston Naming Test 30-Item (BNT) [24] – 30 line drawings of objects are shown individually to the subject, who is asked to name the object.

Statistical Analysis

For the demographic variables, Chi-square analysis was used to examine the distribution of males and females among the three groups while the Kruskall-Wallis test was used to determine whether age and education differed significantly between groups. The Shapiro-Wilk test was used to determine whether the AQ and the individual neuropsychological variables were normally distributed. Since the neuropsychological variables and the AQ did not meet the assumption of normality, Spearman correlation analyses were carried out to assess the linear associations between the AQ and the neuropsychological measures. Correlation values were interpreted as weak (0.00 – 0.39), moderate (0.40 – 0.69), or strong (0.70 – 1.00). Data for DRS-2 and Block Design were only available from smaller subsets of the study sample (DRS-2 n = 79, Block Design n = 55). In order to minimize the impact of floor and ceiling effects from the AD and CN groups on neuropsychological tests, the CN, aMCI, and AD groups were analyzed together. This also allowed for the relationship between the AQ and the individual cognitive tests to be assessed on a continuum of cognitive impairment.

Statistical analyses were carried out using Systat 12.0 (Systat, Inc., San Jose, CA).
Results

The sample for this study ranged in age from 67 to 99 years, with a mean of 83.52±6.51 and a mean educational level of 14.57±2.55 years. The sample included 163 females and 137 males. Of the 300 subjects, 150 were classified as cognitively normal (CN), 83 were classified as amnestic mild cognitive impairment (aMCI), and 67 were classified as Alzheimer’s disease (AD). Demographic characteristics of the clinical groups are reported in Table 1. The groups were not significantly different in terms of age (p = 0.99) or education (p = 0.33). The Chi-square analysis indicated that there was no significant difference in the distribution of males and females among the three clinical groups (p = 0.90).

Correlations between the AQ and the individual cognitive measures are shown in Figures 1 through 6. Each cognitive test was grouped according to its respective domain of assessment (General Cognition – DRS-2, MoCA, MMSE, Clock; Memory – AVLT and BVMT; Executive Function – Trails B, COWAT, Stroop Color/Word; Language – BNT and Animal Fluency; Attention – Trails A, Digit Span Forward, Digit Span Backward; Visuospatial – JLO and Block Design).
Figure 1. Correlation of the AQ with Measures of General Cognition.
Correlation values: MoCA $r = -0.68$, Clock $r = -0.38$, DRS-2 Total $r = -0.72$, MMSE $r = -0.71$; all correlations $p<0.001$
Figure 2. Correlation of AQ with Memory Measures.
Correlation values: AVLT Total r = -0.62, AVLT Delayed Recall r = -0.61, BVMT-R Total r = -0.61, BVMT-R Delayed Recall r = -0.65; all correlations p<0.001.
Figure 3. Correlation of AQ with Executive Function Measures
Correlation values: Trails B $r = 0.53$; Stroop Color/Word $r = -0.51$; Letter Fluency $r = -0.27$; all correlations $p<0.001$. 
Figure 4. Correlation of AQ with Attention Measures
Correlation values: Trails A $r = 0.52$, Digit Span Forward $r = -0.21$, Digit Span Backward $r = -0.37$; all correlations $p<0.001$
Figure 5. Correlation of AQ with Language Measures

Correlation values: Animal Fluency $r = -0.56$, BNT 30-Item $r = -0.44$; all correlations $p<0.001$
Figure 6. Correlation of AQ with Visuospatial Measures

Correlation values: Block Design $r = -0.24$, JLO $r = -0.28$; Block Design $p = 0.08$, JLO $p < 0.001$
The AQ correlated strongly with DRS-2 Total ($r = -0.72$) and the MMSE (-0.71), moderately with the MoCA ($r = -0.68$), and weakly with Clock Drawing ($r = -0.32$). The AQ also demonstrated moderate correlations with measures of memory, as lower performance on the memory measures was associated with greater reported impairment on the AQ (AVLT Total $r = -0.62$, AVLT Delayed Recall $r = -0.61$, BVMT-R Total $r = -0.61$, BVMT-R Delayed Recall $r = -0.65$). Among the executive function measures, the AQ correlated moderately with Trails-B ($r = 0.53$) and Stroop Color/Word ($r = -0.51$), but demonstrated a weak correlation with Letter Fluency ($r = -0.27$). For the measures of attention, the AQ correlated moderately with Trails-A ($r = 0.52$), but demonstrated weak correlations with Digit Span Forward ($r = -0.21$) and Digit Span Backward ($r = -0.37$). Both language measures also correlated moderately with the AQ (BNT 30-Item $r = -0.44$, Animal Fluency $r = -0.56$). For visuospatial function, the JLO demonstrated a weak correlation with the AQ ($r = -0.28$) while Block Design demonstrated no correlation as the correlation value was not statistically significant ($r = -0.24$, $p = 0.08$).
Discussion

The results of this study demonstrate that the AQ, an informant-based assessment, correlates well with several performance-based neuropsychological and cognitive screening tests commonly used in clinical settings. The AQ correlates most strongly with the DRS-2 and the MMSE, and correlates moderately with the MoCA. In the current study, the AQ demonstrated stronger correlations with the MoCA and MMSE than those reported previously [8], possibly due to the larger sample size of the current study. The use of a larger sample size allows for more a precise interpretation of the AQ’s correlation with performance-based neuropsychological and screening tests which strengthens its validity as an informant-based assessment that can be applied and utilized in clinical settings.

Other studies investigating the correlation between informant-based screening measures and objective cognitive tests have found that the AD8 is moderately correlated with the MMSE [4,25], while reported correlation values for the IQCODE and MMSE have varied widely[5]. Galvin et al [4] reported that the AD8 demonstrated weak correlations with neuropsychological tests of specific domains such as memory (WMS Logical Memory and 10-Item Word List) and language (Animal Fluency and BNT); however executive function measures (Trails-B and Digit Symbol) demonstrated moderate correlations with the AD8. Jorm [5] reported on the findings of several studies showing weak correlations between the IQCODE and several neuropsychological measures (WMS Logical Memory, AVLT, Block Design, and Digit Span).

Like the AD8 and IQCODE, the AQ demonstrated some weak correlations with several neuropsychological tests examining specific domains; however several moderate correlations were also noted, particularly with measures of memory and executive function. Given that decreased memory and dual processing skills are hallmark features that direct a clinician to a diagnosis of AD, these results suggest that the AQ is accurately assessing AD-specific cognitive declines. Weak correlations between informant-reported measures and domain-specific neuropsychological tests may be expected to some extent given that informant-based measures often contain items spanning several cognitive domains. Thus, the lack of overlap in the constructs measured by broad informant-based and domain-specific neuropsychological
measures may explain weak correlations between these assessment types. Additionally, as some of these domains, such as visuospatial, are not typically expected to have significant involvement in AD, one would expect the AQ to have lower correlations with these domains than the domains with declines more strongly associated with AD, such as memory and executive function.

With regard to the AQ, the weak and moderate correlations with domain-specific neuropsychological tests may also be due to structure of the measure, as some domains contain more items than others and are thus represented more heavily than others within the AQ total score. The AQ contains several items relating to memory, orientation, and functional ability, but only a few items relating to language and visuospatial domains. This might explain the moderate correlations found for the neuropsychological tests of memory and executive function and the weak correlations with visuospatial tests. However, the imbalance of items within the AQ is due to its initial conceptualization as an instrument designed to detect symptoms associated with aMCI and AD [6,7], which tend to be concentrated in the areas of memory and executive function. The result is that domains such as attention and visuospatial ability are not represented as strongly since these domains tend to be less affected in most cases of aMCI and AD.

Another important consideration is that the AQ relies heavily on reported functional status in activities of daily life. Difficulties noted by family members may not emerge on neuropsychological instruments administered in a more controlled testing environment, which may impact the strength of the correlations between the AQ and neuropsychological measures. However, the moderate and strong correlations in this study provide evidence that informant-reported symptoms on the AQ correspond well to the results of performance-based cognitive assessments.

The results of this study highlight the need to determine how well informant-based screening measures correlate with objective, domain-specific neuropsychological tests that are used to make clinical diagnoses. The correlations observed in this study demonstrate that the AQ correlates well with aspects of cognitive function that are assessed by objective neuropsychological tests, particularly in the domains of memory and executive function. The
moderate correlations noted between the AQ and the neuropsychological tests for memory and executive function, provide evidence that the AQ can accurately assess domains of cognitive function that are of importance when making a clinical diagnosis of aMCI and AD.

While the large sample size was able to add strength to the correlations, one weakness of the study is the ethnically homogenous sample with a majority of participants in the study identifying as white. It is therefore unclear if these results are generalizable to more ethnically diverse populations.

The results of this study provide further evidence to support the validity of the AQ as an instrument for detecting cognitive impairment associated with aMCI and AD. Previous studies have established that the AQ is accurate in differentiating aMCI and AD individuals from cognitively normal individuals [6,7]; however this study demonstrates that the AQ correlates well with commonly-used neuropsychological and cognitive screening measures that are used to make clinical diagnoses of aMCI and AD. Given the AQ’s ease of use and short duration of administration, the results of this study also demonstrate that it could provide a great deal of value to general and geriatric practitioners who desire a screening instrument that is highly predictive of aMCI and AD.
References


