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The Quick Dementia Rating System and its relationship to biomarkers of Alzheimer's disease and neuropsychological performance

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Statement of Ethics: This study protocol was reviewed and approved by the Institutional Review Board at the University of Utah, approval number 00106377. Written informed consent was obtained from participants where applicable. If participants were unable to provide consent, then their assent was obtained and consent was obtained from their legal guardian.

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Abstract

INTRODUCTION: The Quick Dementia Rating System (QDRS) is a brief, patient-reported dementia staging tool that has approximated scores on the Clinical Dementia Rating Scale in patients with Alzheimer's disease (AD). However, no studies have examined its relationship with AD-related biomarkers.

METHODS: One-hundred twenty-one older adults (intact, amnestic Mild Cognitive Impairment, mild AD) completed the QDRS and three biomarkers (amyloid deposition via positron emission tomography, hippocampal volume via magnetic resonance imaging, and apolipoprotein [APOE] ε4 status).

RESULTS: The Total score on the QDRS was statistically significantly related to all three biomarkers (after controlling for age, education, sex, and race), with greater levels of dementia severity being associated with greater amyloid deposition, smaller hippocampi, and having copies of APOE ε4 allele.

DISCUSSION: In participants across the cognitive spectrum, the QDRS showed modest relationships with amyloid deposition, hippocampal volumes, and APOE status. Therefore, the QDRS may offer a cost-effective screening method for clinical trials in AD.

Keywords

Alzheimer's disease; biomarkers; neuropsychological testing; daily functioning

INTRODUCTION

Clinical trials in Alzheimer's disease (AD) have grown tremendously over the past 10 years, which also necessitates the need to identify and screen more potential participants for enrollment. Current screening methods often include extensive cognitive batteries and advanced neuroimaging. However, these screening methods are time-consuming, expensive, and may not generalize to the broader population. For example, an amyloid positron emission tomography (PET) scan can require a visit to a specialized center with technologically-advanced equipment and uniquely-trained personnel, take 2 – 3 hours to complete, and cost $3,000 or more for out of pocket expenses for the individual. More effective, convenient, and less costly screening methods that identify more diverse samples in AD trials are needed.

The Quick Dementia Rating System (QDRS) may fill an important gap as a pre-screening measure for potential participants in AD trials. Developed as a brief, patient-reported measure of dementia severity, the QDRS has approximated Clinical Dementia Rating (CDR) Scale scores [1, 2], the gold standard in AD clinical trials [3]. It has been related to neuropsychological tests [2, 4], and it has demonstrated adequate reliability and validity [2]. As a 10-item rating scale, the QDRS can be completed by the patient or an informant (e.g.,

no specially-trained personnel), it is inexpensive (e.g., free with permission of its developer), it is efficient (e.g., takes 3 – 5 minutes to complete), and it can be remotely collected as a first step in the screening process.

To our knowledge, no studies have assessed the relationship between the QDRS and AD-related biomarkers. Therefore, the current study sought to further validate the QDRS as a screening measure for AD clinical trials by examining its association with common AD biomarkers (amyloid deposition via PET, hippocampal volume via magnetic resonance imaging [MRI], and apolipoprotein [APOE] ε4 status) in older adults who are cognitively intact, amnestic Mild Cognitive Impairment (MCI), or mild AD. It was hypothesized that the QDRS would be related to the three biomarkers, with more dementia severity being associated with more AD pathology. These three biomarkers were chosen because they are three of most commonly used biomarkers in AD research and clinical trials (e.g., collected in Alzheimer's Disease Neuroimaging Initiative [ADNI]). Secondarily, it was expected that greater dementia severity on the QDRS would be related with poorer performance on a brief cognitive battery. Further support for the QDRS as a clinical trial screening measure in AD might allow for safer, more efficient, and less expensive recruitment.

MATERIALS AND METHODS

Participants

One hundred twenty-one older adults were recruited from a cognitive disorders clinic (48.8%) or through the community (51.2%) between 2018 – 2021 to participate in a study of brain imaging and neuropsychological testing across the AD spectrum. Their mean age was 74.2 (SD=5.7, range=65 – 91) years and their mean education was 16.1 (SD=2.4, range=12 – 20) years. Most were Caucasian (98.3%) and 58.7% were female. Mean premorbid intellectual functioning – as measured by the Reading subtest of the Wide Range Achievement Test – 4 (WRAT-4; [5]) – was in the average range (M=109.7, SD=8.5), and self-rating of depression symptoms were minimal on the 15-item Geriatric Depression Scale (M=1.2, SD=1.2; [6]).

Participants were identified in the cognitive disorders' clinic via a medical records review, especially focused on any prior neuropsychological testing, to see they would likely fit into the ADNI criteria for MCI or mild AD. Results of a neurological exam and brain imaging were also considered. Community presentations on memory and aging were conducted to solicit research volunteers, which were more likely to be cognitively intact. However, ~15% of amnestic MCI cases were identified in the community. Confirmation of group assignment was made with the ADNI [7] classification battery, which included the Mini Mental Status Examination [8] (intact and MCI = 24 – 30, AD = 20 – 26), the Clinical Dementia Rating Scale [9] (intact = 0, MCI = 0.5, AD = 0.5 – 1), and the Wechsler Memory Scale – Revised [10] Logical Memory II (intact: ≥9 if education ≥ 16 years, ≥5 if education 8 – 15 years, ≥3 if education 0 – 7 years; MCI and AD: ≤8 if education ≥ 16 years, ≤4 if education 8 – 15 years, ≤2 if education 0 – 7 years).

Participants were included if they were 65 years of age or older and had a knowledgeable informant who would comment on their cognition and daily functioning. Participants were

excluded for medical comorbidities likely to affect cognition (e.g., neurological conditions, current severe depression, substance abuse, major psychiatric conditions), inability to complete MRI or PET, inability to complete cognitive assessments, and being enrolled in an anti-amyloid clinical drug trial. Additional exclusion criteria included a score of >5 on the 15-item Geriatric Depression Scale, a Clinical Dementia Rating score of ≥2, or a Mini Mental Status Examination score of <20. Sixty-seven individuals were excluded for a variety of reasons (e.g., neurological condition = 10, unable to complete MRI = 10, did not fit into any group = 9, clinical results did not indicate AD = 9, medical condition = 8, elevated Geriatric Depression Scale = 7, psychiatric condition = 3, Mini Mental Status Examination score of <20 = 3, Clinical Dementia Rating score of ≥2 = 3, under 65 years of age = 2, allergic reaction that might interfere with PET = 2, no study partner = 1).

Procedure

Procedures were approved by the local Institutional Review Board. Following informed consent/assent, participants underwent testing with the ADNI battery and other neuropsychological testing at a baseline visit. They returned 10.7 days (SD=19.2) to receive an MRI of the brain, and 19.5 days (SD=16.9) to receive amyloid PET imaging of the brain using ^{18}F-Flutemetamol and a blood draw to determine APOE ε4 status.

Measures

The QDRS [2] is a patient or informant reported dementia staging tool with 10 questions that rate the patient's functioning in memory and recall, orientation, problem-solving, activities outside the home, functioning at home, personal hygiene, behavior and personality changes, language and communication, mood, and attention. Scores range from 0 to 30, with higher scores indicating more cognitive impairment. It has two subdomains, Cognitive and Behavioral, which account for 40% and 60% of the questionnaire, respectively. Although the QDRS can be completed by either the patient or informant, in this study, informants completed this measure on their respective patients.

The Repeatable Battery for the Asssessment of Neuropsychological Status (RBANS) [11] is a brief neuropsychological testing battery comprised of 12 subtests used to calculate 5 Index scores: Immediate Memory Index, Visuospatial/Constructional Index, Attention Index, Language Index, and Delayed Memory Index, and a Total Scale score. Using normative data, these Index scores are age-corrected standard scores (M=100, SD=15), with higher scores indicating better cognition.

The WRAT- 4 Reading subtest [5], in which a participant reads irregular words, was administered to assess premorbid intellect. Using normative data, age-corrected standard scores are generated (M=100, SD=15), with higher scores indicating higher premorbid intellect.

MRI

MRI was acquired on a 3.0-T Siemens Prisma scanner with a 64-channel head coil. Structural data were acquired using an MP2RAGE sequence (TR = 5000, TE = 2.93, acquired sagittally, resolution=1 × 1 × 1 mm) to obtain high quality whole brain 1mm

isotropic T1 images with improved signal homogeneity in ~7 minutes. All MRI scans were examined for the presence of common artifacts, including motion, susceptibility, and distortion, and were determined to be of sufficient quality for quantitative analysis. All data were processed on the same workstation using FreeSurfer image analysis suite v6.0 (http://surfer.nmr.mgh.harvard.edu/) to estimate total estimated intracranial and hippocampal volumes. Technical details are described previously [12–14]. To address head size differences, hippocampal volumes have been adjusted by estimated total intracranial volume. Left and right hemispheric volumes were summed to create total hippocampal volume adjusted by total intracranial volume.

Amyloid Imaging

Amyloid imaging was performed using ^{18}F-Flutemetamol which is a radioactive diagnostic agent indicated for PET imaging of the brain to estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment. ^{18}F-Flutemetamol was produced under PET cGMP standards and conducted under an approved Food & Drug Adminstration Investigational New Drug application (IND). Twenty minutes of emission imaging was performed 90 minutes after the injection of approximately 185 mBq (5 mCi) of ^{18}F-Flutemetamol. A General Electric Discovery PET/Computed Tomography (CT) 710 (General Electric Healthcare) was used in this study. This PET/CT scanner has full width at half-maximum spatial resolution of 5.0 mm and excellent performance characteristics [15, 16]. Volumes of interest were automatically generated by using the CortexID Suite analysis software (General Electric Healthcare). ^{18}F-Flutemetamol binding was analyzed using a regional semi-quantitative technique described by Vandenberghe, Van Laere [17] and refined by Thurfjell, Lilja [18]. The CortexID Suite software generates, semi-quantitative regional (prefrontal, anterior cingulate, precuneus/posterior cingulate, parietal, mesial temporal, lateral temporal, occipital, sensorimotor, cerebellar grey matter, and whole cerebellum) standardized uptake value ratios (SUVRs) normalized to the pons. A composite SUVR in the cerebral cortex was generated automatically and normalized to the pons using the CortexID Suite software [19].

APOE Genotyping

Polymerase Chain Reaction and Fluorescence Monitoring using hybridization probes for APOE genotyping was conducted using whole blood samples. Results were dichotomized as being APOE ε4 allele carriers (both hetero- and homozygous) or non-carriers.

Data Analysis

Continuous biomarker data (hippocampal volumes and amyloid SUVR), as well as RBANS indexes, were correlated (via Pearson correlations) with QDRS Total score and the two subdomain scores, after controlling for age, education, sex, and race. For dichotomous/ordinal data (APOE ε4 status), biserial correlations were calculated between those with at least one ε4 allele and those with no ε4 alleles and QDRS Total score and subdomains. To protect against multiple comparisons, a false discovery rate was calculated for each biomarker analysis at 0.05.

RESULTS

As can be seen in Table 1, 54 of the participants were classified as cognitively intact, 35 were classified as amnestic MCI, and 32 were classified as AD. Demographically, those with AD were significantly older than the other two groups ($p<0.001$), and the intact individuals had significantly more years of education than those with MCI ($p=0.006$). There were not differences between the groups on sex, race, premorbid intellect, or depression ($p>0.05$). All three groups were significantly different on the QDRS Total score ($p<0.001$), as well as the Behavioral ($p<0.001$) and Cognitive ($p<0.001$) subdomains, with the cognitively intact participants having the lowest/best scores, followed by the MCI participants, and then the AD participants (Table 1). There were also group differences for the biomarkers: 1) hippocampal volumes ($p<0.001$, intact>MCI>AD), 2) cerebral amyloid ($p<0.001$, intact<MCI, AD), and 3) APOE ε4 alleles ($p<0.001$, AD, MCI>intact). Although there were differences between groups on age and education, QDRS scores, and biomarkers, these differences were not considered in the correlational analyses, as the groups were pooled.

Correlations with Biomarkers

For the entire sample, using a false discovery rate, total hippocampal volumes were significantly correlated with the QDRS Total score, as well as both the Behavioral and Cognitive subdomains (see Table 2). All significant correlations went in the expected direction, with larger hippocampal volumes being associated with lower total and subdomain scores on the QDRS.

Cerebral amyloid (SUVR) was significantly correlated with QDRS Total score, as well as both the Behavioral and Cognitive subdomains (see Table 2). All correlations went in the expected direction, with greater amyloid deposition being associated with higher QDRS scores.

When individuals were dichotomized as having either no ε4 alleles or having one/two copies of ε4, then these two groups were statistically significantly different on the QDRS Total score and the Cognitive subdomain (see Table 2). For each statistically significant difference, those with no ε4 alleles had lower scores on the QDRS than those with one/two ε4 alleles.

Correlations with Cognitive Tests

RBANS Index scores were also significantly correlated with the QDRS Total scores, as well as the Cognitive and Behavioral subdomains (see Table 2). The Delayed Memory Index had the strongest correlation with the QDRS, however, all were statistically significant. All correlations went in the expected direction, with higher RBANS scores being correlated with lower QDRS scores. Conversely, WRAT-4 scores did not correlate with QDRS Total score or either of the subdomains.

DISCUSSION

The current study examined the relationships between the QDRS and three biomarkers associated with AD in a sample of older adults who are cognitively intact or have amnestic

MCI or or mild AD. Consistent with our hypotheses, scores on the collateral-rated QDRS were significantly correlated with all three biomarkers and in the expected direction (i.e., greater dementia severity was associated with more amyloid deposition, smaller hippocampi, and more APOE ε4 alleles). To our knowledge, this is the first study to investigate the relationship between biomarkers and the QDRS, and it further validates this instrument as part of the screening process for clinical trials in AD.

Since previous studies have correlated QDRS and CDR scores [2], the addition of correlation with AD biomarkers adds to the use of this measure. For example, greater dementia on the CDR have been associated with greater cerebral amyloid [20, 21], smaller hippocampal volumes [22–24], and the presence of APOE e4 [25, 26]. As such, the current results with the QDRS, a proxy of CDR scores, are consistent with expectations. However, the QDRS has some potential advantages over the CDR, including that the former is briefer (e.g., <5 minutes for QDRS vs. 45+ minutes for CDR), only needs a patient or informant (vs. informant and patient for the CDR), and does not require an experienced and certified rater to administer (which the CDR does).

Although there is no prior information about the QDRS and biomarkers, the QDRS has been linked to some neuropsychological test scores. Galvin [2015] reported modest correlations between the QDRS and a brief battery of cognitive tests. In a larger and more cognitively diverse sample, correlations between the QDRS and test scores ranged from −0.28 to −0.60 (with higher QDRS scores being associated with poorer cognition). In the current study, correlations with the Total score on the QDRS ranged from −0.26 to −0.67 across RBANS scores. In these studies, the strongest relationships occurred between the QDRS and measures of global cognition (e.g., Mini Mental Status Examination in Galvin r = −0.60, RBANS Total Scale in current study r = −0.59). More recently, Galvin et al. [2020] found that the QDRS negatively correlated with a new cognitive measure of executive functioning (r= −0.56). One of the limitations of the RBANS in the current study is that it does not assess executive functioning. Nonetheless, across multiple studies, the QDRS has been related to cognitive test scores.

The current study also reports on both of the subdomains of the QDRS: cognitive and behavioral. In this cohort, the cognitive subdomain of the QDRS was more strongly correlated with each of the three biomarkers, as well as the RBANS Indexes, than the behavioral domain. Since the cognitive subdomain is comprised of items rating the patient's memory, orientation, decision-making, and language, the high correlations make sense. Future studies using the QDRS as a screening measure might consider focusing on the cognitive subdomain, which only contains four items. Conversely, the slightly longer 6-item behavioral subdomain was less strongly related to the other markers of AD. For example, the correlations with the RBANS were relatively weaker (e.g., RBANS Total Scale: cognitive subdomain r = −0.68, behavioral subdomain r = −0.48; Fisher's r to z transformation z=2.35, p=0.02). The behavioral subdomain contains items on daily functioning (e.g., activities outside the home, home and hobby activities, personal hygiene) and psychiatric symptoms (e.g., personality changes, mood), which would seem to be less related to cognitive test scores and biomarkers. Nonetheless, these sub-scores could more effectively evaluate the

specific domains affected in each patient, and thus allow for more focused screening and intervention.

This study has limitations. First, the sample had limited demographic and diagnostic diversity, being largely white and well-educated, which could limit the generalizability of these findings to more diverse populations. Second, the range on the 15-item Geriatric Depression Scale was restricted to 0–5, hence reducing the influence of depression-related cognitive impairment. Since depression can cause cognitive dysfunction [27, 28], it is unclear if these results would remain in a more depressed sample. Third, the current sample only included individuals with normal cognition, amnestic MCI, and mild AD, as initially diagnosed in a clinical setting and then confirmed by the ADNI criteria. There is some concern about how accurately the ADNI criteria identify AD-specific cases [29, 30]. Additionally, the sample sizes for the MCI and mild AD groups were relatively small, and the generalizability of these results to their respective populations needs further validation. It is also unclear how these results would generalize to more advanced AD or non-AD neurodegenerative conditions (e.g. Lewy Body Dementia, vascular dementia). Finally, the current study did not include a measure of tau. Research suggests that tau may have a mediating effect on amyloid and cognition [31]. As tau PET imaging technology becomes more widespread, future research should examine its relationship with the QDRS. Despite these limitations, the current results provide additional support for using the QDRS in clinical and non-clinical evaluations of older adults with suspected AD, as well as a key screening measure in AD clinical trials. Although additional validation is needed, the current study further validated the QDRS as a safer, less expensive, and more efficient alternative screening measure. For example, compared to the widely-used cognitive screening measure, the Mini Mental Status Examination, the QDRS can be remotely administered (vs. in-person administration), it is self-administered by the patient or collateral (vs. needing a trained rater), it is free with permission of its developer (vs. purchasing it from its publisher), it assesses aspects of cognition, behavior, and daily functioning (vs. only cognition), and it approximates the Clinical Dementia Rating scale.

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Conflict of Interest Statement:

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Data Availability Statement:

As this project was funded by the National Institutes of Health, this data will be made available upon request from the Corresponding Author.

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Table 1.

Sample information.

Variable	Total Sample	Cognitively Intact	MCI	Mild AD	Group Differences
N	121	54	35	32	
Age (years)	74.2 (5.7)	72.5 (4.8)	73.4 (5.1)	77.8 (6.2)	F=10.4, p<0.001 c>a,b
Education (years)	16.1 (2.4)	16.7 (2.1)	15.1 (2.6)	16.2 (2.3)	F=5.3, p=0.006 a>b
Sex (% female)	58.7%	61.1%	57.1%	56.3%	n.s.
Race (% Caucasian)	98.3%	100.0%	94.3%	100.0%	n.s.
MMSE	26.9 (3.2)	29.4 (0.8)	26.5 (1.9)	23.0 (2.7)	F=128.4, p<0.001 a>b>c
WMS-R Logical Memory I	8.7 (5.5)	13.4 (3.9)	5.7 (3.1)	4.0 (3.0)	F=93.4, p<0.001 a>b>c
WMS-R Logical Memory II	6.6 (5.9)	12.0 (3.9)	3.1 (3.2)	1.3 (1.4)	F=145.7, p<0.001 a>b>c
GDS	1.2 (1.2)	0.9 (1.1)	1.5 (1.4)	1.2 (1.1)	F=2.7, p=0.07
QDRS Total Score	3.4 (3.4)	0.5 (0.8)	4.4 (2.6)	7.0 (2.7)	F=104.6, p<0.001 c>b>a
QDRS Cognitive Subdomain	1.6 (1.5)	0.2 (0.4)	2.1 (0.9)	3.3 (1.1)	F=178.1, p<0.001 c>b>a
QDRS Behavioral Subdomain	1.8 (2.0)	0.4 (0.6)	2.3 (2.0)	3.6 (1.9)	F=51.5, p<0.001 c>b>a
Hippocampal Volume (cm3)	3.8 (0.8)	4.2 (0.8)	3.6 (0.5)	3.2 (0.9)	F=19.8, p<0.001 a>b>c
SUVR	0.6 (0.2)	0.5 (0.1)	0.8 (0.2)	0.8 (0.1)	F=57.9, P<0.001 c>b,a
APOE ε4 (% with one or more alleles)	52%	30%	66%	75%	X2=20.2, p<0.001 b,c>a
WRAT-IV Reading	109. 7 (8.5)	110.5 (7.3)	107.2 (10.2)	110.9 (8.2)	F=2.1, p=0.13
RBANS Immediate Memory	88.4 (22.3)	107.4 (13.2)	77.7 (14.8)	67.8 (14.0)	F=96.3, p<0.001 a>b>c
RBANS Visuospatial Constructional	99.3 (17.4)	106.8 (13.6)	95.0 (15.0)	91.5 (19.9)	F=10.9, p<0.001 a>b,a
RBANS Language	95.2 (14.4)	104.1 (11.5)	91.3 (11.1)	84.2 (12.8)	F=31.6, p<0.001 a>b>c
RBANS Attention	100.0 (16.4)	108.3 (13.4)	96.3 (14.6)	89.9 (16.3)	F=17.7, p<0.001 a>b,c
RBANS Delay Memory	82.6 (29.3)	110.4 (12.0)	67.5 (18.6)	52.2 (11.4)	F=200.4, p<0.001 a>b>c
RBANS Total Scale	91.5 (22.0)	110.6 (13.3)	81.6 (11.1)	70.1 (14.3)	F=128.4, p<0.001 a>b>c

Note. AD = Alzheimer's disease, GDS = Geriatric Depression Scale, MCI = Mild Cognitive Impairment, MMSE = Mini Mental Status Examination, SUVR = standardized uptake value ratio, QDRS = Quick Dementia Rating System, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, WMS-R = Wechsler Memory Scale – Revised, WRAT-IV = Wide Range Achievement Test - IV. MMSE, WMS-R, GDS, and QDRS scores are raw scores. RBANS and WRAT-IV scores are age-corrected standard scores (M=100, SD=15). In final column, F-, x^2, and p-values reflect comparisons between cognitively intact, MCI, and AD groups, and post-hoc comparisons are based on Least Significant Tests, with a=cognitively intact, b=MCI, and c=AD.

Table 2.

Correlations between QDRS and biomarkers and RBANS scores.

Biomarker or Score	QDRS Cognitive Subdomain	QDRS Behavioral Subdomain	QDRS Total Score
Hippocampal Volume (cm^3)	r=−0.39, p<0.001	r=−0.24, p=0.01	r=−0.32, p<0.001
SUVR	r=0.54, p<0.001	r=0.32, p<0.001	r=0.44, p<0.001
APOE ε4 (% with one or more alleles)	r=0.35, p<0.001	r=0.13, p=0.15	r=0.24, p=0.01
WRAT4 Age-Corrected Standard Score	r=−0.09, p=0.34	r=−0.13, p=0.16	r=−0.12, p=0.20
RBANS Immediate Memory Index	r=−0.65, p<0.001	r=−0.48, p<0.001	r=−0.58, p<0.001
RBANS Visuospatial Constructional Index	r=−0.28, p=0.002	r=−0.23, p=0.01	r=−0.26, p=0.004
RBANS Language Index	r=−0.46, p<0.001	r=−0.40, p<0.001	r=−0.45, p<0.001
RBANS Attention Index	r=−0.44, p<0.001	r=−0.35, p<0.001	r=−0.41, p<0.001
RBANS Delayed Memory Index	r=−0.76, p<0.001	r=−0.54, p<0.001	r=−0.67, p<0.001
RBANS Total Scale Score	r=−0.68, p<0.001	r=−0.48, p<0.001	r=−0.59, p<0.001

Note. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, SUVR = standardized uptake value ratio, QDRS = Quick Dementia Rating System, WRAT = Wide Range Achievement Test. All correlations control for age, education, sex, and race.