Specific depression dimensions are associated with a faster rate of cognitive decline in older adults

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Abstract

Introduction: Understanding the relationship between different depression presentations and cognitive outcome may elucidate high-risk sub-groups for cognitive decline.

Methods: In this study we utilized longitudinal data from the National Alzheimer’s Coordinating Center (NACC) on 16,743 initially not demented older adults followed every 12 months for an average of 5 years. Depression dimensions were defined based on the 15-item Geriatric Depression Scale (GDS-15), that is, dysphoric mood, Withdrawal-Apathy-Vigor (WAV), anxiety, hopelessness, and subjective memory complaint (SMC).

Results: After adjustment for sociodemographic and clinical covariates, SMC and hopelessness were associated with faster decline in global cognition and all cognitive domains and WAV with decline executive function. Dysphoric mood and anxiety were not associated with a faster cognitive decline in any of the cognitive domains.

Discussion: Different depression dimensions had different associations with the rate of cognitive decline, suggesting distinct pathophysiology and the need for more targeted interventions.

KEYWORDS
cognitive decline, depression dimensions, older adults

1 INTRODUCTION

Neuropsychiatric symptoms, including affective presentations, are common across all stages of dementia including the pre-clinical stage. There is compelling evidence for the associations between depressive symptoms, as well as sub-syndromal or sub-threshold depression and dementia. Although the evidence for syndromic depression, predicting dementia risk, and cognitive decline is relatively robust, the role of distinct affective presentations is yet to be elucidated. The few longitudinal studies examining associations of dimensions of depression with poor incident cognitive outcomes have found that specific dimensions (such as apathy and dysphoria) are linked differentially to incident mild cognitive impairment (MCI) and dementia. Identification of specific dimensions of depression are crucial for defining accurate neurobiology, outcome trajectories, and specific treatment selection. Indeed, symptom-based depression sub-types have been identified as differentially responding to treatment. For example, three symptom clusters (core emotional symptoms, insomnia, and atypical depressive symptoms) were characterized among depressed participants and shown to vary in their response to treatment (ie, duloxetine outperformed escitalopram in treating core emotional symptoms). In another study, mood and cognitive symptoms...
were more effectively treated with escitalopram, whereas neurovegetative symptoms responded better to nortriptyline.9

Here, we utilized the wealth of longitudinal data from a large sample (N = 16,743) of initially non-demented subjects enrolled in the National Alzheimer’s Coordinating Center (NACC), to study the relationship between depression dimensions and decline in global cognition and in specific cognitive domains over a period of 5 years. The association of depression and cognitive impairment has been explored previously in the well-characterized cohort of NACC participants.5 Although the available results support the notion of depression as a risk factor for accelerated cognitive decline, this study investigates the associations of specific depression dimensions with global cognitive decline and with decline in specific cognitive domains. Identifying predictors of cognitive decline in depression may serve as a step toward personalized medicine by better identifying subgroups of patients who are most at risk for cognitive compromise.

2 METHODS

2.1 Data source and sample derivation

Data are drawn from the National Alzheimer’s Coordinating Center Uniform Data Set (NACC-UDS). Recruitment, participant evaluation, and diagnostic criteria are detailed elsewhere.11 Briefly, beginning in September 2005, participants were followed prospectively from 39 past and present National Institute on Aging (NIA) funded Alzheimer’s Disease Centers (ADCs), located in university medical centers throughout the United States. Ongoing recruitment is through clinician referral, self-referral, referral by family members, community outreach efforts, or active recruitment of volunteers who wish to contribute to the studies. Participants are followed at ≈12-month intervals using standard evaluations and reassessment at each visit. Written informed consent was provided by all participants and their informants and approved by local institutional review boards (IRBs). The NACC-UDS provides systematic information on demographics, behavioral status, cognitive testing, medical history, family history, clinical impressions, and diagnoses using standardized forms.

Cognitive status (ie, cognitively normal [CN]; MCI; impaired but not diagnosed with MCI [INM]; and demential) are assessed at each visit in the NACC-UDS. Procedures of clinical diagnosis can be from that of a consensus panel or a single physician according to each ADC’s diagnostic protocol; however, each ADC adheres to standardized clinical criteria outlined by the UDS coding guidebook.12 Since its inception in 2005, the NACC-UDS has undergone two revisions: UDS Version 2 and 3. A crosswalk study has established conversion factors that allow for harmonization of test scores that have undergone the revisions.13

The sample selection process is summarized in Figure 1. Data used in the current study comprise all participants who were enrolled in NACC-UDS between September 2005 (start date of the UDS) and December 2019 data freeze (N = 42,022). To be eligible for the current study, participants had to be 60 years of age or older at baseline, have had at least one follow-up visit, had a diagnosis of non-dementia as determined by clinician consensus and a Clinical Dementia Rating (CDR) score of 0 or 0.5 at baseline, and non-missing 15-item Geriatric Depression Scale (GDS-15) results. In longitudinal analysis, telephone follow-up visits were excluded because cognitive assessments were performed during in-person visits only.

2.2 Measures

2.2.1 Construction of global cognitive scores and cognitive domain scores

All participants were administered a standardized battery of common neuropsychological tests at each study visit. Prior to UDS 3,
neuropsychological tests included Mini Mental Status Exam (MMSE), WMS-R Logical Memory Immediate (LM-IA) and Delayed Recall (LM-IIA), WMS-R Digit Span forward and backward, Wechsler Adult Intelligence Scale-Revised Digit Symbol Coding (WAIS-R DSC), Trail Making Test (TMT) Part A and B, category fluency in animals and vegetables, and Short Form of the Boston Naming Test (BNT). Several proprietary tests from UDS 2 were replaced in UDS 3 with non-proprietary tests. We applied published conversion factors to these tests so that all available data could be used.13 Neuropsychological tests were categorized into the following domains: memory (Wechsler Memory Scale-Revised [WMS-R] Logical Memory Immediate [LM-IA] and Delayed Recall [LM-IIA]), attention (WMS-R Digit Span forward and backward, Trail Making Test [TMT] Part A), language (category fluency in animals, vegetables, Short Form of the Boston Naming Test [BNT]), and executive functions (TMT Part B).14 Cognitive composite scores were computed following the existing literature.15 For each test, we computed a z-score at baseline. A composite score for each cognitive domain at baseline was constructed by averaging the z-scores for each test in that domain. A global cognition measure was calculated by averaging the z-scores from all tests. Although missing values for individual tests were allowed, domain score was set to missing if more than half of tests in that domain were missing. Global score was set to missing if more than half of all tests were missing. Requiring complete data on all tests did not change study results. For follow-up assessments, mean and standard deviation (SD) from the baseline scores were used to construct corresponding z-scores for each cognitive domain and global cognition.

2.2.2 Defining GDS-15 dimensions

Participants’ depressive symptoms were measured using the 15-item Geriatric Depression Scale (or GDS-15).16 The GDS-15 is a self-report measure of yes/no questions pertaining to the presence of depression symptoms. Answers to five items were reversed such that higher total GDS score would be indicative of more severe depression. We used the domains defined by Adams et al17 on GDS-30 based on results from a factor analysis and adapted to the GDS-1518 as following: Dysphoric mood, items 1, 3, 4, 5, 7, 11, 15; Withdrawal-Apathy-Vigor (WAV), items 2, 9, 13; Anxiety, item 6; Subjective Memory Complaint (SMC), item 10; and Hopelessness, items 8, 12, 14 (Figure 2, Table S1).

2.3 Demographics and clinical characteristics

Demographic characteristics included age, sex, race (White, Black, vs other), ethnicity (Hispanic/Latino vs other), and years of education. Cardiovascular risk factors included history of diabetes, hypertension, and hypercholesterolemia, ascertained by self-report or clinician assessment. Participants’ function was measured using the Functional Assessment Questionnaire (FAQ) reported from interviews with study partners.19 Apolipoprotein E (APOE) genotype for participants who are willing to provide samples was reported by the ADCs. We constructed an indicator variable for any APOE e4 allele and an indicator for missing APOE information.

2.4 Statistical analyses

Multi-variable analyses were performed using linear mixed models (LMMs) for global cognition and cognitive domain scores separately. Our main independent variables are GDS-15 dimension scores, time, and the interaction terms between GDS-15 dimension scores and time, entered into the model as fixed effects. We used UDS visit to measure time (which was highly correlated with time since baseline, \( r = 0.97 \)). The coefficients of the GDS-15 dimension scores estimated baseline differences in the cognitive outcome by the GDS-15 dimension score; Our main interest was in the coefficients on the interaction terms between GDS-15 dimension scores and time, which estimated...
If the coefficient of the interaction term was negative, this indicated a faster rate of decline in cognition for those with worse GDS-15 dimension scores. If the coefficient on the interaction term was positive, this indicated a slower rate of decline in cognition with worse GDS-15 dimension scores. We hypothesized that higher GDS-15 dimension scores would be associated with a faster rate of cognitive decline. In secondary analyses, we stratified the sample by MCI and non-MCI at baseline to examine whether the initial cognitive status affected the associations of depression dimensions with cognitive decline.

Covariates included in the LMM were baseline age, sex, race/ethnicity, years of education, baseline functional level (i.e., FAQ), NACC-UDS version, and indicators for history of diabetes, hypertension, and hypercholesterolemia and APOE genotype. All models included individual random intercepts and random slopes to allow individual differences at baseline as well as overall rate of change over time. Because we estimated models for five separate outcomes, statistical significance was set a priori at $P < .01$.

### 3 | RESULTS

#### 3.1 | Baseline sample characteristics

Table 1 describes the characteristics of the sample. At baseline, participants were about 74 years of age, a majority (59%) were female, White (81%), and had an average of 15 years of education; 62% were cognitively normal, 38% were MCI or were cognitively impaired but non-MCI. Average MMSE was 28.34 ± 1.96, which is consistent with a sample that is not demented at baseline; FAQ was 1.28 ± 2.92, reflecting little impairment in activities of daily living; GDS-15 was 1.66 ± 2.23 indicating relatively little clinical depression. About 13% of participants had diabetes, 52% hypertension, and 53% high cholesterol. Of those who agreed to have APOE genotyping (84% of the sample), 34% had at least one APOE ε4 allele. On average, participants had five annual assessments.

#### 3.2 | Multivariate results

Mixed-regression estimation results on the relationships between GDS-15 dimension scores and global and cognitive domains are shown in Table 2.

#### 3.2.1 | Association between GDS-15 dimension scores and cognition at baseline

As shown in Table 2, Higher scores in the WAV dimension scores were associated with a higher score in the episodic memory domain (coefficient estimate $b = 0.054 ± 0.008, P = .0001$), but worst performance in attention ($b = -0.021 ± 0.006, P = .0008$).
## TABLE 2  Adjusted associations of depression dimensions with rate of decline in global cognition and specific cognitive domains at baseline and over time including all subjects

|                                | Global Cognition Coefficient | Memory Coefficient | Attention Coefficient | Language Coefficient | Executive Function Coefficient |
|--------------------------------|-------------------------------|--------------------|------------------------|----------------------|-------------------------------|
|                                | (SE)                          | (SE)               | (SE)                   | (SE)                 | (SE)                          |
|                                | 95% CI                        | 95% CI             | 95% CI                 | 95% CI               | 95% CI                        |
|                                | p                             | p                  | p                      | p                    | p                             |
| NACC Visit                     | −0.018                        | 0.021              | −0.030                 | −0.038               | −0.051                        |
|                                | (0.001)                       | (0.002)            | (0.001)                | (0.002)              | (0.002)                       |
|                                | [−0.021, −0.015]**            | [0.017, 0.025]**    | [−0.033, −0.027]**     | [−0.041, −0.034]**    | [−0.056, −0.047]**            |
|                                | < .0001>                      | < .0001>           | < .0001>               | < .0001>             | < .0001>                      |
| BASELINE DIFFERENCES           |                               |                    |                        |                      |                               |
| Dysphoric Mood                 | −0.009                        | −0.005             | −0.012                 | −0.009               | −0.018                        |
|                                | (0.004)                       | (0.007)            | (0.005)                | (0.005)              | (0.008)                       |
|                                | [−0.018, −0.001]              | [−0.019, 0.008]    | [−0.022, −0.001]       | [−0.019, 0.002]      | [−0.033, −0.003]              |
|                                | < .024>                       | <.435>             | <.25>                  | <.120>               | <.020>                        |
| Withdrawal-Apathy-Vigor (WAV)  | 0.002                         | 0.054              | −0.021                 | −0.001               | −0.020                        |
|                                | (0.005)                       | (0.008)            | (0.006)                | (0.007)              | (0.009)                       |
|                                | [−0.008, 0.0118]              | [0.038, 0.071]     | [−0.034, −0.009]       | [−0.014, 0.012]      | [−0.038, −0.002]**            |
|                                | < .724>                       | < .001>            | < .0008>               | < .874>              | < .272>                       |
| Anxiety                        | −0.003                        | 0.001              | −0.004                 | −0.005               | −0.094                        |
|                                | (0.014)                       | (0.024)            | (0.018)                | (0.019)              | (0.026)                       |
|                                | [−0.030, 0.025]               | [−0.045, 0.048]    | [−0.039, 0.031]        | [−0.042, 0.032]      | [−0.145, −0.044]**            |
|                                | < .855>                       | < .960>            | < .819>                | < .800>              | < .0003>                      |
| Subjective memory complaint    | −0.063                        | −0.208             | 0.004                  | −0.076               | −0.005                        |
|                                | (0.010)                       | (0.017)            | (0.013)                | (0.014)              | (0.019)                       |
|                                | [−0.083, −0.042]**            | [−0.242, −0.174]** | [−0.021, 0.029]        | [−0.103, −0.049]**   | [−0.038, 0.037]               |
|                                | < .0001>                      | < .001>            | < .7559>               | < .0001>             | < .9800>                      |
| Hopelessness                   | −0.003                        | 0.014              | −0.010                 | −0.004               | −0.014                        |
|                                | (0.005)                       | (0.009)            | (0.006)                | (0.006)              | (0.012)                       |
|                                | [−0.012, 0.006]               | [−0.005, 0.033]    | [−0.023, 0.002]        | [−0.017, 0.008]      | [−0.037, 0.009]               |
|                                | < .530>                       | < .139>            | < .111>                | < .517>              | < .232>                       |
| LONGITUDINAL DIFFERENCE        |                               |                    |                        |                      |                               |
| Dysphoric Mood                 | 0.0005                        | −0.0002            | 0.0006                 | 0.0006               | 0.0009                        |
|                                | (0.001)                       | (0.002)            | (0.001)                | (0.001)              | (0.002)                       |
|                                | [−0.002, 0.003]               | [−0.004, 0.003]    | [−0.002, 0.003]        | [−0.002, 0.003]      | [−0.003, 0.004]               |
|                                | < .699>                       | < .899>            | < .579>                | < .701>              | < .618>                       |
| Withdrawal-Apathy-Vigor (WAV)  | −0.002                        | −0.003             | −0.002                 | −0.0002              | −0.007                        |
|                                | (0.001)                       | (0.002)            | (0.001)                | (0.0012)             | (0.002)                       |
|                                | [−0.005, 0.0006]              | [−0.007, 0.001]    | [−0.005, 0.0002]       | [−0.004, 0.003]      | [−0.011, −0.003]**            |
|                                | < .125>                       | < .170>            | < .075>                | < .905>              | < .0005>                      |
| Anxiety                        | 0.004                         | 0.008              | −0.0004                | 0.004                | 0.007                         |
|                                | (0.004)                       | (0.006)            | (0.004)                | (0.005)              | (0.006)                       |
|                                | [−0.004, 0.012]               | [−0.004, 0.019]    | [−0.008, 0.007]        | [−0.006, 0.014]      | [−0.005, 0.019]               |
|                                | < .295>                       | < .181>            | < .914>                | < .418>              | < .256>                       |

(Continues)
### TABLE 2 (Continued)

| Subjective memory complaint | Global Cognition Coefficient (SE) 95% CI | Memory Coefficient (SE) 95% CI | Attention Coefficient (SE) 95% CI | Language Coefficient (SE) 95% CI | Executive Function Coefficient (SE) 95% CI |
|-----------------------------|------------------------------------------|---------------------------------|-----------------------------------|----------------------------------|-------------------------------------------|
|                             | −0.027 (0.002) [-0.032, -0.021]**         | −0.020 (0.004) [-0.028, -0.011]** | −0.018 (0.003) [-0.024, -0.013]** | −0.031 (0.003) [-0.038, -0.024]** | −0.018 (0.004) [-0.027, -0.009]**         |
|                             | < .0001>                                 | < .0001>                        | < .0001>                          | < .0001>                         | < .0001>                                  |
| Hopelessness                | −0.007 (0.001) [-0.009, -0.005]**         | −0.015 (0.002) [-0.019, -0.011]** | −0.007 (0.001) [-0.009, -0.005]** | −0.007 (0.001) [-0.009, -0.004]** | −0.016 (0.002) [-0.021, -0.011]**         |
|                             | < .0001>                                 | < .0001>                        | < .0001>                          | < .0001>                         | < .0001>                                  |

**COVARIATES**

- **MCI vs non-MCI at Baseline**: −0.4356 (0.0097) [-0.4545, -0.4166]**
  - Global Cognition Coefficient: −0.7098 (0.0160) [-0.7410, -0.6786]**
  - Memory Coefficient: −0.3185 (0.0119) [-0.3418, -0.2951]**
  - Attention Coefficient: −0.317 (0.0127) [-0.3459, -0.3010]**
  - Language Coefficient: −0.4349 (0.0173) [-0.4726, -0.4048]**
  - Executive Function Coefficient: −0.4387 (0.0173) [-0.4726, -0.4048]**
  - Age 70-79 (Reference = Age 60-69): −0.181 (0.009) [-0.198, -0.164]**
  - Age ≥80: −0.426 (0.011) [-0.447, -0.405]**
  - Female: 0.093 (0.008) [0.171, 0.220]
  - Black (Reference = White): −0.392 (0.012) [-0.415, -0.369]**
  - Other Race Groups: −0.316 (0.019) [-0.354, -0.278]**
  - Hispanic: −0.365 (0.017) [-0.398, -0.332]**

(Continues)
**TABLE 2**  (Continued)

|                          | Global Cognition Coefficient (SE) 95% CI | Memory Coefficient (SE) 95% CI | Attention Coefficient (SE) 95% CI | Language Coefficient (SE) 95% CI | Executive Function Coefficient (SE) 95% CI |
|--------------------------|------------------------------------------|---------------------------------|-----------------------------------|----------------------------------|---------------------------------------------|
| Years of schooling       | 0.05 ± 0.001 (0.048, 0.053)*** < .0001 | 0.053 ± 0.002 (0.049, 0.057)** < .0001 | 0.052 ± 0.001 (0.049, 0.055)** < .0001 | 0.047 ± 0.0012 (0.043, 0.050)** < .0001 | 0.061 ± 0.002 (0.056, 0.065)** < .0001 |
| UDS V3 vs V2             | −0.129 ± 0.004 (−0.136, −0.122)** < .0001 | −0.273 ± 0.008 (−0.288, −0.258)** < .0001 | −0.017 ± 0.005 (−0.027, −0.008)** < .0001 | −0.079 ± 0.005 (−0.089, −0.069)** < .0001 | −0.042 ± 0.008 (−0.057, −0.026)** < .0001 |
| Diabetes                 | −0.04 ± 0.012 (−0.063, −0.017)** < .0006 | 0.050 ± 0.019 (0.014, 0.019) | −0.105 ± 0.014 (−0.132, −0.077)** < .0007 | −0.021 ± 0.015 (−0.051, 0.009) | −0.119 ± 0.020 (−0.158, −0.081)** < .0001 |
| Hypertension             | −0.039 ± 0.008 (−0.055, −0.024)** < .0001 | −0.013 ± 0.013 (−0.038, 0.012) | 0.06 ± 0.009 (−0.079, −0.041)** < .0001 | −0.027 ± 0.010 (−0.047, −0.006)** < .0001 | −0.073 ± 0.013 (−0.099, −0.047)** < .0001 |
| Hypercholesterolemia     | −0.001 ± 0.008 (−0.017, 0.014) | −0.010 ± 0.012 (−0.033, 0.015) | 0.013 ± 0.009 (−0.006, 0.031) | −0.006 ± 0.010 (−0.026, 0.014) | −0.017 ± 0.013 (−0.008, 0.043) |
| FAQ                      | −0.251 ± 0.0145 (−0.279, −0.222)** < .0001 | −0.374 ± 0.023 (−0.420, −0.329)** < .0001 | −0.236 ± 0.023 (−0.271, −0.202)** < .0001 | −0.244 ± 0.017 (−0.281, −0.207)** < .0001 | −0.377 ± 0.027 (−0.431, −0.326)** < .0001 |
| Any APOE e4              | −0.039 ± 0.009 (−0.056, −0.022)** < .0001 | −0.173 ± 0.014 (−0.199, −0.145)** < .0001 | −0.025 ± 0.010 (−0.046, −0.005) | −0.019 ± 0.011 (−0.041, 0.003) | −0.074 ± 0.015 (−0.102, −0.045)** < .0001 |
| APOE missing             | −0.019 ± 0.011 (−0.041, 0.003) | −0.007 ± 0.018 (−0.042, 0.029) | −0.051 ± 0.014 (−0.078, −0.024)*** < .0050 | −0.021 ± 0.015 (−0.050, 0.008) | −0.085 ± 0.019 (−0.123, −0.04766)** < .0001 |

**P < .01; ***P < .001.

language (b ± SE = −0.076 ± 0.014, P < .0001). Finally, a higher degree of hopelessness was not associated with any of the cognitive domains.

3.2.2 Association between GDS-15 dimension scores and longitudinal cognitive decline

As presented in Table 2 and Figure 3, global cognition and all cognitive domains significantly deteriorated over time (all P’s < .0001). Higher scores in the WAV dimension were associated with a faster rate of decline in executive functions (b ± SE = −0.007 ± 0.002, P = .0005), but not with other cognitive domains or with global cognition. A positive answer on the memory complaint dimension and a higher score in the hopelessness dimension score were associated with a faster rate of decline in all cognitive outcomes (P < .0001). However, greater dysphoria or a positive answer in the anxiety question was not associated with decline in global cognition or with decline in any of the cognitive domains.
Secondary analyses showed that in the MCI group, subjective memory complaint was associated with a faster decline in all aspects of cognition (all \(P\)'s < .0001) and hopelessness was associated with greater decline in global cognition and episodic memory (\(b \pm SE = -0.004 \pm 0.002, P = .024\) and \(b \pm SE = -0.010 \pm 0.004, P = .003\), respectively), whereas WAV, dysphoria, and anxiety were not associated with any of the cognitive outcomes (Table S2). Among non-MCI subjects, WAV and hopelessness were associated with decline in all cognitive domains (all \(P\)'s < .01), but dysphoria, anxiety, or subjective memory complaint was not (Table S3).

4 I DISCUSSION

In this study we examined the association of depression dimensions with cognitive decline in a large national longitudinal study of older adults followed for an average of 5 years, who were neither demented nor clinically depressed at baseline. Our results showed that hopelessness, subjective memory complaint, and WAV were associated with faster rate of decline in global cognition and specific cognitive domains, whereas anxiety and dysphoria were not. These results highlight that depression dimensions vary distinctively with regard to their associated cognitive trajectories.

The one memory item in the GDS-15 scale is consistent with what was described in the literature as subjective memory complaint (SMC), a state in which an individual complains about difficulty with cognitive performance while still being able to compensate for the deficiencies and not reaching the level of objective impairment. Accordingly, there is evidence for the value of SMC as a predictor of cognitive decline, and some longitudinal studies show that people with SMC have a higher risk of dementia. Subjective memory decline is associated with AD markers including cortical atrophy, especially in the medial temporal lobe, that is, entorhinal cortex, hippocampus, anterior cingulate, and pre-cuneus and higher amyloid beta (A\(_\beta\)) deposition. However, there is also substantial evidence suggesting that SMC is not related to incident dementia and cognitive decline. Some of these conflicting results may be explained by confounders, including demographics and the settings from which the subjects are recruited. In people with a higher level of function and education, who may perform cognitive testing at a ceiling level, self-reports of cognitive impairment may in fact be an early indicator of signs of decline. Although in younger people SMC may be largely influenced by personality, mood, and anxiety, in older adults these complaints may harbor a marker for evolving impairment. Moreover, whereas SMC in the community is more likely to represent a normative aging process, those presenting to a memory clinic like the volunteers of the present study, represent an enriched population more likely to be in the course of a pathological course with associated incipient cognitive decline.

Although our results did not show any significant long-term decline with dysphoria, the hopelessness dimension was associated with a faster rate of decline in all cognitive domains. This may be explained at least in part by the possibility that the hopelessness dimension in this study included more severe depressive symptoms, that is, feelings of helplessness, worthlessness, and hopelessness. Hopelessness is defined as one's negative bias toward the future as opposed to the negative bias toward the self (worthlessness) or the world. Hopelessness, more recently included in the definition of core depressed mood in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), has been identified as the key factor linking depression to suicidal behavior and is reported to be associated with poor outcomes in health and social functioning, as well as medical conditions such as congestive heart failure and heart attack, independently
Apathy, the most common behavioral disturbance in dementia, is a syndrome whose core features encompass behavioral, affective, and cognitive aspects defined as diminished motivation, initiation, and interest, and blunting of emotions. Apathy has also been shown to be associated with a greater risk for developing MCI and AD. Our results showed that what we defined as Withdrawal-Apathy-Vigor (WAV), was associated with greater global decline specifically in executive function. Consistent with our results, in our study, the neurobiology of apathy involves impaired prefrontal cortical recruitment of limbic activity, a process that is essential for motivated behavior. In addition, hypoperfusion in striatal and insular areas represents neural correlates of apathy in AD patients.

Anxiety was not associated with decline in global cognition or in any cognitive domain. A meta-analysis of longitudinal studies showed associations of anxiety with incident cognitive impairment and dementia in community-based samples, but, consistent with our findings, no associations were found in clinical samples of MCI subjects. Another study in older adults with type 2 diabetes also showed no association between anxiety and cognitive decline. Of interest, mid-life repetitive thinking, a behavior highly related to anxiety, was reported previously to be associated with a lower risk for dementia three decades later, and individuals reporting higher neuroticism, which is primarily characterized by high anxiety, had better cognitive performance, indicating that the role of anxiety in the dementia process is complex and has yet to be elucidated.

In secondary analyses, we stratified the sample by baseline cognitive status. For both those who initiated the study with normal cognition or with MCI, hopelessness was significantly associated with cognitive decline. For those with MCI at baseline, but not for participants who had normal cognition at baseline, subjective memory complaint was strongly associated with a decline in global cognition and all cognitive domains. Moreover, only among participants with normal cognition, WAV was associated with a faster rate of cognitive decline. These results suggest that the initial cognitive status is relevant to the role of specific depression dimensions in cognitive decline.

Our study has strengths, including its longitudinal design, large sample of participants, detailed data available on cognition, which permitted examination of association of specific cognitive domains with specific depression dimension scores, and a broad range of potential confounders. Nonetheless, the NACC-UDS study participants are enrolled through referral-volunteer mechanisms, which vary among different ADCs and also within each ADC over time. As a result, this cohort is not representative of the general population, but is rather an enriched sample with risk factors for dementia. The sample's low average GDS-15 scores suggest that observed associations may be valid in a population with relatively low number of depression symptoms. Yet, our results may not be applicable to the clinically depressed population. Another limitation of the study is that many of the covariates were self-reported rather than directly measured. Some of the confounding factors were under-reported in our sample. The prevalence of diabetes and hypertension in our sample was less than reported in national statistics, and hyperlipidemia was close to national statistics. APOE ε4 allele status was not available for 17% of the study, but exclusion of participants that did not have APOE ε4 allele data did not alter the results. In our population ≈30% had at least one APOE ε4 allele, which is slightly higher than reported nationally (≈25%), National Institutes of Health, highlighting the clinic-based nature of this NACC cohort. Our study is also limited by the use of the GDS-15 as a clinical biomarker of depression dimensions. Despite being a validated depression scale in different populations, GDS-15 is limited by how it can characterize different depression dimensions compared to an in-depth clinical examination. For example, it is possible that the null results for the association of anxiety with cognitive decline may be due to the psychometric limitations of a single-item question. However, SMC was also measured by one dichotomous question, yet it was found to have highly significant associations with cognitive decline.

In conclusion, our study highlights the associations of accelerated cognitive decline with depression dimensions, even when the degree of depressive symptoms is not sufficiently robust to cause significant dysfunction or fulfill criteria of clinical depression. Identification of specific affective profiles may improve the ability to predict poor cognitive trajectories in older adults. Despite the yearning for identifying objective biomarkers to guide, diagnose, assess, and monitor treatment outcomes in psychiatric disorders, this endeavor so far has remained largely unsuccessful. One alternative direction has been using other forms of data including digital data to fill in this gap with the specific advantages that they offer, including widespread use, availability, and the potential to capture more granular behavioral markers toward more in depth behavioral phenotyping.

ACKNOWLEDGEMENTS
This work was supported by NACC-UDS (U01 AG016976) and Alzheimer’s Disease Research Center at Mount Sinai (U01 P50 AG005138 P30 AG066514), and National Institutes of Health (NIH) grants R01 AG053446, R01 AG051545, R01AG061093 PI for Dr. Beeri. Drs. Zhu, Sano, Grossman also are supported by the Department of Veterans Affairs, Veterans Health Administration. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

CONFLICTS OF INTEREST
Dr. Sano serves as a board member of Alzheimer’s Association, International Psychogeriatric Association, National Association of VA
were reported for the other authors.

SYneos. No other potential conflicts of interest relevant to this article:

Avenir, vTv, Biogen, BioXce, F. Hoffman LaRoche, and Other/DSMB:

Research Foundations; and as a consultant on trial design for Eisai,

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

How to cite this article: Soleimani L, Schnaider Beeri M, Grossman H, Sano M, Zhu CW. Specific depression dimensions are associated with a faster rate of cognitive decline in older adults. Alzheimer’s Dementia. 2022;14:e12268. https://doi.org/10.1002/dad2.12268