Development and validation of the Vanderbilt Informant-Based Subjective Cognitive Decline Questionnaire (Vanderbilt I-SCD)

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ABSTRACT

Objectives: Subjective cognitive decline (SCD), a self-reported concern about one's memory or thinking, is emerging as a potential early marker of unhealthy brain aging, recognized by the recent operationalized definition of SCD. However, SCD has limitations, such as overreporting concerns. Informants (loved ones) can provide valuable insight to mitigate these limitations, but existing informant-based SCD (I-SCD) tools were developed prior to the recent operationalized definition and therefore fail to capture all relevant SCD criteria. In this study, we developed an I-SCD questionnaire and validated the questionnaire by comparing it with measures of objective cognition and biomarkers of Alzheimer's disease (AD).

Methods: The I-SCD questionnaire was created using data from 537 informants (62±13 years, 69% female) of 458 cognitively unimpaired (CU; 68±8 years, 55% female) and 79 cognitively impaired older adults (CI; 75±9 years, 51% female) from the Vanderbilt Memory and Alzheimer's Center Participant Registry. Informants all completed an I-SCD protocol including the Informant-Everyday Cognition scale and the Informant-Cognitive Changes Questionnaire. Latent variable modeling was used for item selection. Participants in the validation study were drawn from an independent cohort, the Vanderbilt Memory & Aging Project, including 176 CU (73±7 years, 41% female) and 132 CI older adults (CI; 73±8 years, 44% female) and their loved ones. All completed the new I-SCD questionnaire, a self-SCD questionnaire, objective cognitive assessment, and brain MRI with a subset undergoing fasting lumbar puncture for acquisition of AD biomarkers ($A\beta_{42}$ and tau). Area under the receiver operating characteristic (AUROC) curve was used to measure the utility of the I-SCD tool for diagnostic discrimination. Regressions adjusting for age, sex, education, race/ethnicity, depressed mood, and apolipoprotein ε4 (APOE-4) status related I-SCD score to objective cognition, self-SCD, and AD biomarkers.

Results: The Vanderbilt I-SCD Questionnaire (Vanderbilt I-SCD) includes 25 items and fulfills all operationalized SCD criteria. Within the validation cohort, the total score of the I-SCD significantly discriminated between CU and CI (AUC = 0.802, CI = 0.741-0.863). Linear regressions indicated increasing total I-SCD score was significantly associated with greater self-SCD, worse objective cognition in the areas of memory, executive functioning, and language, and increasing levels of amyloidosis and tau deposition (all p-values <0.05). Regression analyses stratified by cognitive diagnosis suggested these findings are driven by the CI group, whereas total I-SCD score appears related to self-SCD only in the CU group (OR= 0.59, P = 0.012).

Conclusions: Results indicate that the Vanderbilt I-SCD discriminates between diagnostic statuses (CU vs. CI). Vanderbilt I-SCD score was also strongly associated with multiple markers of unhealthy brain aging and AD pathology. This finding was most notable among participants in the prodromal phase of AD (mild cognitive impairment), which aligns with previous research highlighting that I-SCD is most useful in this phase compared to preclinical AD. Overall, findings support the utility of the Vanderbilt I-SCD as a useful screening tool or as a tool to monitor cognitive status in patients with prodromal AD.

Keywords: informant, subjective cognitive decline, Alzheimer's disease

BACKGROUND

Alzheimer's disease (AD) is characterized by the presence of amyloid beta plaques and tau neurofibrillary tangles and accounts for 60-80% of clinical dementia diagnoses ("2019 Alzheimer's Disease Facts and Figures," 2019). The prevalence of AD is an estimated 5.8 million individuals in the United States, amounting to a cumulative cost of $290 billion in annual spending on AD and dementias of other etiologies in the U.S. ("2019 Alzheimer's Disease Facts and Figures," 2019). Although there is no known cure, early detection promotes care planning, reduction of risky behaviors, and cost savings. Additionally, early cognitive treatment services with a speech-language pathologist have been shown to promote better outcomes (Bayles et el., 2014). Early detection involves identification of unhealthy brain aging before the onset of symptoms, in what is known as the preclinical stage of AD.

Subjective cognitive decline (SCD), or the self-perceived decline of one's own cognition, has been identified as a potential early marker of unhealthy brain aging in preclinical AD (Mendonca et al., 2016). Research has shown that it is associated with biomarkers of AD (Studart & Nitrini, 2016) at the preclinical phase, or prior to the onset of objective or observable clinical symptoms. Specifically, SCD has been linked with atrophy in the medial temporal lobes and other neocortical regions (Jessen et al., 2006; Saykin et al., 2006), elevated presence of amyloid plaques observed in functional neuroimaging (Amariglio et al., 2012; Perrotin et al., 2012), and more recently, increased tau deposition seen in neuroimaging (Buckley et al., 2017). In addition to biomarkers, SCD has been shown to predict a longitudinal decline in performance on objective cognitive assessments (Archer et al., 2007; Ehrensperger et al., 2014; Gifford et al., 2015; Nicholas et al., 2017; Rattanabannakit et al., 2016) and increased risk of progression to

clinical AD (Jessen, Wolfsgruber, et al., 2014; Mendonca et al., 2016; Rabin et al., 2017; Studart & Nitrini, 2016).

Given this mounting data supporting the utility of SCD, efforts have been made to develop an operationalized definition of SCD for research and clinical purposes. The SCD International Working Group (SCD-I) has suggested an operationalized definition of SCD describing a collection of features suggestive of underlying AD (Jessen, Amariglio, et al., 2014). These criteria include: presence of subjective decline in memory (rather than other domains of cognition), onset in the last 5 years, age of onset of SCD of at least 60 years, concern/worry associated with SCD, and feeling of worse performance than others in the same age group. The association between SCD and AD biomarkers is strongest when the measure of SCD meets the operationalized criteria (Sanchez-Benavides et al., 2018). Additional contributing features of SCD that support an underlying AD pathology include confirmation of cognitive decline by a loved one, presence of the APOE-ε4 genotype, and biomarker evidence for AD. Many measures of SCD were published before these criteria, and therefore do not contain items to meet all operationalized criteria. However, a recently published semi-structured interview for SCD assessment, the subjective cognitive decline interview (SCD-I; Miebach et al., 2019), includes all SCD-plus criteria, a subset of these operationalized SCD criteria that has been associated with increased likelihood of the presence of preclinical AD (Jessen, Amariglio, et al., 2014). SCD is now recognized as a factor along the clinical spectrum of AD as per the recent National Institute on Aging and Alzheimer's Association (NIAA-AA) framework for diagnosing and identifying AD (Jack et al., 2018) because of all of this data supporting its utility. This framework provides syndromal staging of the cognitive continuum, in which individuals progress from cognitively unimpaired to mild cognitive impairment (MCI) to dementia, along with numeric clinical staging

progressing from Stage 1 (cognitively unimpaired) to Stage 6 (severe dementia). Cognitively unimpaired individuals who have preclinical AD (Stage 2) may report SCD in the absence of objective cognitive impairment (Jack et al., 2018), but SCD may present the earliest clinical manifestation of the pathology.

Although there is much evidence supporting SCD as an early marker of unhealthy brain aging, limitations persist. First, previous studies suggest that low cognitive awareness (i.e., when subjects report less difficulties than their informants) may represent a very early form of anosognosia and serve as a specific indicator of preclinical AD. It is possible that subtle changes to cognition do not occur until the late stage of preclinical AD, thus the patient may not become "aware" of these changes until too late in the disease, resulting in lack of awareness (Rabin et al., 2017). This lack of awareness may contribute to SCD being an unreliable approach to measuring cognitive status. Second, there are non-AD factors that drive SCD, including depression, anxiety, other mood factors, physical health, and other co-morbid conditions to AD. Specifically, individuals with depression may experience changes in cognition on both subjective (Grut et al., 1993; Rabin et al., 2017) and objective measures (Rabin et al., 2017), so SCD may reflect a different underlying pathology separate from AD. SCD has also been shown to be overestimated in individuals with anxiety (Denney & Prigatano, 2019; Rabin et al., 2017). Furthermore, personality type may influence self-perception of cognition, as SCD is more closely associated with objective cognitive performance in adults who possess lower levels of neuroticism (Mulligan et al., 2018). In other words, high levels of neuroticism are associated with heightened response to stressful stimuli and thus higher likelihood of endorsing complaints. Another non-AD factor that drives SCD is chronic health conditions, such as diabetes or cardiovascular disease. Individuals with chronic physical health difficulties are more likely to endorse cognitive

complaints (Jackson & Cooper, 2017). Lastly, the findings linking SCD to biomarkers, cognition, or diagnosis are not consistent. For example, Valech and colleagues (2015) showed that SCD is not significantly correlated with amyloidosis or tau deposition, and that it is not as highly correlated with objective cognitive performance as informant-based SCD. As a result of its inconsistency, previous literature has suggested that SCD by itself is not a clinical marker of preclinical AD (Edmonds et al., 2014) and suggested instead that we consult loved ones of individuals with suspected cognitive changes to add valuable information. Thus, one way to mitigate these limitations and bolster the predictive properties of SCD is by using informant-based reports of SCD, or a loved one's perception of the patient's cognition, especially considering informant reports may be less susceptible to these non-AD factors (Edmonds et al., 2014).

Informant SCD

The addition of informant-based SCD (I-SCD), or report of cognitive status by a loved one, may mitigate SCD limitations including anosognosia, influence of non-AD factors, and inconsistent relationship with objective cognition and biomarkers. Thus, the inclusion of I-SCD may improve the clinicians' and researchers' ability to predict conversion to AD. Previous literature has shown that I-SCD better differentiates between normal cognition and unhealthy brain aging as compared to SCD (Kim et al., 2019; Yim et al., 2017) as well as between normal cognitive aging and diagnostic conversion to MCI or AD dementia (Gifford et al., 2014; Mendonca et al., 2016). Gifford and colleagues (2014) compared self-complaint, informant complaint, and mutual complaint (presence of complaint from both participant and informant) in individuals with normal cognition. They found that I-SCD was comparable to SCD in individuals

with normal cognition, but mutual complaint was more predictive than either self or informant complaint alone. However, in individuals with MCI, informant complaint was equivalent to mutual complaint in its predictiveness of diagnostic conversion to AD, and both were more predictive than SCD (Gifford et al., 2014). In a comprehensive systematic review, Mendonca and colleagues (2016) found that endorsement of an individual's self-complaint by an informant doubles the risk of progression to MCI or dementia after 3.5 years of follow-up and is associated with a 5-fold increase to the risk of progression to MCI after 6.7 years of follow-up. Collectively, previous literature shows that I-SCD has strong prognostic utility in identifying early cognitive decline and predicting conversion to AD.

In addition to its association with cognitive status, I-SCD is associated with biomarkers of AD. Specifically, I-SCD has been associated with increased evidence of amyloidosis and tau deposition, as measured by cerebrospinal fluid (Valech et al., 2015). Structurally, I-SCD is related to smaller brain volumes in multiple regions known to be affected by early AD pathology (Archer et al., 2007; Dong et al., 2018; Fyock & Hampstead, 2015). More recent functional (resting state) neuroimaging work suggests that I-SCD is linked with altered functional connectivity (Dong et al., 2018).

Beyond these clinical and biomarker associations, one strength of I-SCD is that it is less susceptible than SCD to non-AD factors. First, previous research has shown that the presence of informant complaint is strongly associated with impairment on objective cognitive assessment measures (Archer et al., 2007; Nicholas et al., 2017; Rami et al., 2014; Rattanabannakit et al., 2016). Second, it is less likely to be influenced by mood or personality factors than self-complaint. In a large sample of nondemented community-dwelling adults, Slavin and colleagues (2010) showed that both participant and informant complaints are weakly correlated with

participant depression, anxiety, and neuroticism scores, but informants were more likely to endorse complaint in the presence of objective cognitive decline. After controlling for these participant characteristics, I-SCD was associated with global cognitive decline, functional decline, and diagnostic conversion over four years (Slavin et al., 2010).

Current measures of I-SCD

Despite the value of I-SCD in predicting cognitive decline, there are relatively few standardized measures that assess I-SCD, and existing measures have limitations. **Table 1** shows existing standardized measures of I-SCD. The most widely used informant-based questionnaire, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), is a 26-item questionnaire in which the informant rates changes in everyday cognition that have occurred over the past 10 years. However, overall score on this questionnaire has been shown to be affected by informant characteristics such as depression and anxiety as well as by relationship between informant and patient (Jorm et al., 2004). Additionally, in a review examining three empirical studies, Christie (2018) found that the questionnaire has exhibited low specificity in screening out individuals who would not develop AD, especially in studies that used lower cut-off values. Several studies have used shorter versions of this questionnaire (Ehrensperger et al., 2014; Sikkes et al., 2011; Sikkes et al., 2010) but have not matched the psychometric properties of the original version. Another widely used measure is the Subjective Cognitive Decline Questionnaire (SCD-Q), which has versions for both the patient (called "MyCog") and his or her informant (called "TheirCog"). The combination of these questionnaires (using information from both the patient and informant) has been shown as more effective than informant-only report (Rami et al., 2014). Additional standardized measures, such as the Cognitive Change Index

(CCI), Deterioration Cognitive Observe (DECO), and the Seoul Informant Report Questionnaire for Dementia (SIRQD) have not been studied longitudinally (Ramlall et al., 2013; Rattanabannakit et al., 2016; Yim et al., 2017). The DECO and SIRQD have not been normed on English speakers (Ramlall et al., 2013; Yim et al., 2017), and research has shown that questions from the AD8 are susceptible to cultural bias (Shiong Lim et al., 2011).

The final measure listed in **Table 1**, Everyday Cognition with an informant version, has relatively strong psychometric properties with some minor limitations (Tomaszewski Farias et al., 2008). When Tomaszewski Farias and colleagues (2008) validated this measure on a medium-sized pilot cohort including informants of individuals with normal cognition, MCI, and dementia, its Everyday Global Function scale was associated with the Blessed Dementia Rating Scale, Clinical Dementia Rating Scale, Mini-Mental State Examination, and clinical diagnosis, and the other scales showed significant associations but not consistently. Additionally, each of the three clinical diagnostic groups performed differently in each domain (Tomaszewski Farias et al., 2008). Adapted versions including shorter versions (Marshall et al., 2014; Tomaszewski Farias et al., 2011) and a Spanish version (Russo et al., 2018) have been created. However, as with all other measures, this measure has limitations. First, despite its original purpose of measuring informant report of functional aspects of cognition (Tomaszewski Farias et al., 2008), it is used in the present study as a measure of informant-report SCD. Second, despite its relatively strong psychometric properties overall, it is weakly correlated with age and education (Tomaszewski Farias et al., 2008). Third, this measure is longer (i.e., 39 items) than many of the measures previously discussed. This measure will be discussed in further detail in the Methods section.

Table 1. Current standardized I-SCD measures.

Measure	Description	Limitation(s)

Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)	26-item questionnaire that measures changes in everyday cognitive functioning over the previous 10 years; 5-point Likert scale (Sikkes et al., 2011; Sikkes et al., 2010)	Affected by informant depression and anxiety and quality of the relationship (Jorm et al., 2004); Low specificity (especially at lower cut-off values (Christie, 2018); 16-item short Dutch form is influenced by age (Sikkes et al., 2011)
Subjective Cognitive Decline-Questionnaire (SCD-Q)	24-item questionnaire including "MyCog" and "TheirCog," which asses perceived subjective decline in memory, language, and executive functions over the last two years (Rami et al., 2014)	Informant report measure ("TheirCog") not as predictive as both measures combined "TheirCog" and "MyCog;" (Rami et al., 2014)
Cognitive Change Index (CCI)	20-item tool used to assess the perception of cognitive decline in memory, executive function, and language domains from both self and informant perspectives with 5-point Likert scales (Rattanabannakit et al., 2016)	Has not been studied longitudinally; Validated on relatively young (67.8±11.2 years) sample; Validation study did not include psychological conditions or personality traits (Rattanabannakit et al., 2016)
Deterioration Cognitive Observe (DECO)	19-item Likert scale that assesses changes in behavior (activity level, semantic and visual memory, memory for places, events and procedures, visuospatial performance, and new skill learning) over the past year (Ramlall et al., 2013)	Has not been studied longitudinally or validated in the United States or on English speakers; Utility study had homogenous sample with high participant refusal rate and did not use clinical diagnosis as comparison (Ramlall et al., 2013)
AD8	8-item forced-choice (yes/no) scale in which informant rates changes in memory, problem-solving abilities, orientation, and daily activities (Shuang Wan et al., 2016)	Susceptible to cultural bias (Shiong Lim et al., 2011)
Seoul Informant Report Questionnaire for Dementia (SIRQD)	15-item informant questionnaire on cognitive impairment (Yim et al., 2017)	Has not been studied longitudinally or normed in the United States or on English speakers; Combination of SIRQD with Subjective Memory Complaints Questionnaire (patient-reported SCD measure) is more accurate than SIRQD alone in screening for MCI and overall cognitive disorder (Yim et al., 2017)
Cognitive Difficulties Scale (CDS)	41-item scale measuring the frequency of everyday cognitive difficulties (Jefferson et al., 2016)	Informant report has been shown to significantly predict MCI but not AD (Buelow et al., 2014)
Cognitive Change Checklist (3CL)	28-item informant rating questionnaire with four nonoverlapping scales including memory, executive, language, and remote recall (Schinka et al., 2009)	Development and initial validation study was based on sample that was primarily White in race and did not include participants with heterogenous MCI diagnoses (e.g., amnestic; Schinka et al., 2009)
Everyday Cognition	39-item scale that measures functional activities within memory, language, visuospatial, and executive function subdomains (Tomaszewski Farias et al., 2008)	Intended to measure functional aspects of cognition rather than I-SCD (Tomaszewski Farias et al., 2008); Relatively strong psychometric properties overall, but weak correlation with age and education (Tomaszewski Farias et al., 2008); Length of 39 items
I-SCD=informant-based subjective cognitive decline		

Purpose

The purpose of this project was to examine how informants of older adults endorse different questions related to the assessment of a loved one's memory or cognitive abilities. The first aim (development study) was to identify a subset of I-SCD questions in a community-based cohort of middle-aged and older adults that distinguished normal cognition from cognitive impairment. Our first hypothesis was that using latent variable modeling techniques, we will identify a subset of questions to measure I-SCD that will reliably discriminate these two groups. The second aim (validation study) was to determine the validity of the I-SCD questionnaire by cross-sectionally relating it to SCD, objective cognitive measures, and unhealthy brain aging biomarkers including cerebrospinal fluid biomarkers and brain imaging metrics. Our second hypothesis was that the I-SCD questionnaire will moderately to strongly relate with SCD, objective cognitive measures, and unhealthy brain aging biomarkers.

METHODS

Aim 1- Development study: Data from Informant-Based Study of Memory in Adults: A Survey Study (I-MASS)

This study is part of a parent study called *Memory in Adults: A Survey Study* (MASS) at the Vanderbilt Memory and Alzheimer's Center (VMAC), in which cognitively unimpaired (CU) and cognitively impaired (CI) older adults were asked to rate their memory abilities to assess self-perceptions of cognition. Cognitive impairment was determined from participants' score on the Telephone Interview for Cognitive Status (TICS), a telephone-based objective cognitive screening measure with a score range of 0-41. Participants who scored 33 or above were classified as CU and participants who scored 26-32 were classified as CI. Individuals scoring within the dementia range or who self-reported a diagnosis of dementia were excluded (TICS score of 25 or below, or clinical diagnosis of dementia).

Participants

In I-MASS, all participants from MASS were contacted via mailing and asked to identify an informant to answer questions about the participant's cognitive status to determine the informant's perception of the participant's memory. Inclusion criteria for the MASS participants were being 50 years of age or older and having a primary language of English. Exclusion criteria included a history of psychiatric illness (e.g., schizophrenia, bipolar disorder), other neurological illness (e.g., epilepsy, multiple sclerosis), or major head trauma with significant loss of consciousness. Participants also completed the Center for Epidemiological Studies Depression Scale (CESD; Radloff, 1997) to assess depressed mood. For the purpose of the current study, we reached out to all participants in MASS to ask if participants had a loved one that could answer

questions about the participant's cognition. Inclusion criteria for the informants were an age of 18 or older and an ability to answer questions about the participant's cognition. Informants represented any individual identified by the participant, including spouses, adult children, other relatives, or friends.

Measures

Informants were sent a mailing or a link to an online survey. The measures included a cover letter describing the study, consent form, I-SCD questionnaires, and a brief demographic information form for the informant.

The I-SCD questionnaires utilized for the current study included the informant-based versions of the Cognitive Changes Questionnaire (I-CCQ; Jefferson et al., 2016) and Everyday Cognition (I-ECog; Tomaszewski Farias et al., 2008). Descriptions of each questionnaire are listed in **Table 2.**

The I-CCQ was derived from frequently used questions about cognition (Jefferson et al., 2016). It includes 73 items that assess changes in memory and cognition compared to the participant's past cognition, cognition of same-age peers, and ability to complete daily tasks. Items take the format of "yes/no" or 3-point Likert scales ("always" to "never," or "major problem" to "no problem"). A higher score indicates greater I-SCD.

The I-ECog has been found to be a valid measure of determining functional status (Tomaszewski Farias et al., 2008) and has been adapted in multiple previous studies (Marshall et al., 2014; Russo et al., 2018; Tomaszewski Farias et al., 2011). It includes 39 items measuring functional activities within memory, language, visuospatial skills, and executive function subdomains. Items take the format of a 4-point Likert scale ("better or no change" to "consistently much worse"). A higher score indicates greater I-SCD.

The self-report SCD protocol in MASS was comprised of a 45-item questionnaire previously developed by Gifford and colleagues (2019) in order to measure the participants' perceptions of their own cognitive status.

Questionnaires with >15% missingness were discarded. For questionnaires with <15% missingness, the total score was prorated.

Table 2: I-MASS measures of I-SCD

Measure	Purpose	Sub-domain(s)	Description	Range
Cognitive Changes Questionnaire (I-CCQ)	Assess changes in memory and cognition in comparison to the participant's past cognition, current cognition of same-age peers, and ability to complete daily tasks	Memory	59 items rated on a 2-point (yes/no) scale 10 items about frequency of problem rated on a 3-point ("always," "sometimes," "never") scale 4 items comparing memory to past on a 3-point scale ("major problem," "some minor problems," "no problems")	14-85 Higher scores indicate greater I-SCD
Everyday Cognition (I-ECog)	Measures functional activities within memory, language, visuospatial, and executive function subdomains	Memory, language, executive function	39 items measuring decline rated on a 4-point Likert scale (1= better or no change; 4 = consistently much worse)	39-156 Higher scores indicate greater I-SCD
I-MASS: informant-based Memory and Adults: A Survey Study; I-SCD=informant-based subjective cognitive decline; I-CCQ=Cognitive Changes Questionnaire; I-ECog=Everyday Cognition				

Statistical Analyses

Descriptive statistics were calculated for participant age, sex, education, race/ethnicity, CESD score, and SCD score, as well as informant age, sex, education, and score on the I-SCD questionnaires. Diagnosis (CU versus CI) was based on participants' TICS score as described above. Mann-Whitney U tests and Pearson's Chi-Square tests were used to calculate differences between groups for continuous and categorical measures, respectively.

Latent variable modeling techniques were used to select items. First, we inspected items. Items with local dependence, high levels of missingness, consistent endorsement, or duplicate content were removed. Local dependence refers to items that require a certain response to

another item, such as requesting an elaboration on a "yes" answer from a previous item. High missingness refers to items that have more than 5% missing data across the entire sample. Consistent endorsement refers to items with more than 90% of responses endorsing the same response option. Duplicate content refers to items that ask the same questions exactly or with slightly different wording.

To select from groups of items with similar content, we used item response theory (IRT) to select the best items. IRT is a statistical procedure used in previous SCD and I-SCD questionnaire development studies (e.g., Gifford et al., 2015; Sikkes et al., 2011; Tomaszewski Farias et al., 2011) to identify items that most reliably measure the latent variable of I-SCD based upon item information curves. Items were selected with a peaked information function to identify items ideal for the questionnaire.

Then, factor analytic models assessed unidimensionality of the latent trait (I-SCD); items with poor trait-fit were removed. Repeated factor analytic models were run until no items with poor fit remained. As a last step, the "bank" of selected items was then inspected to confirm that items fulfill all operationalized SCD criteria (Jessen, Amariglio, et al., 2014). If criteria were not filled, items were selected to be reintroduced and a factor analysis was completed again. The final selection of items will represent the Vanderbilt I-SCD questionnaire (Vanderbilt I-SCD).

From the resulting items, a total score could be calculated. Additionally, we aimed to identify cognitive subdomains (i.e., memory, executive function, language). Experts reviewed each item and indicated what domain an item should correspond to.

Analyses were conducted using R statistical software.

Aim 2- Validation study: Data from Memory & Aging Project (VMAP)

The Vanderbilt I-SCD developed in Aim 1 was validated in an independent cohort - the participants and informants of the Vanderbilt Memory & Aging Project (VMAP; Jefferson et al., 2016).

Participants

VMAP is a longitudinal cohort focused on examining the link between vascular risk factors and cognitive impairment, previously described (Jefferson et al., 2016). Briefly, participants were included in VMAP if they were English-speaking and had adequate auditory and visual acuity for testing. Exclusion criteria of VMAP included any contraindications for magnetic resonance imaging (MRI) and history of any of the following: neurological illness, stroke, heart failure, major psychiatric illness, head injury with loss of consciousness >5 minutes, chronic obstructive pulmonary disease, or a systematic or terminal illness that could impact participation in follow-up examinations. Informants were included if they knew the participant a minimum of 2 years at study enrollment with weekly contact and knowledge of participant's cognitive and functional abilities.

Measures

For the purposes of the current project, we leveraged assessments including an SCD and I-SCD protocol, a comprehensive neuropsychological assessment protocol, a brain MRI, participant mood measure, and a fasting blood draw during the VMAP baseline visit (Jefferson et al., 2016). A subset of participants also completed an optional lumbar puncture for cerebrospinal fluid (CSF). A description of each VMAP measure is provided in **Table 3.** Participants underwent a detailed clinical interview for diagnostic determination (CU vs. CI) at a prior screening visit, including a medical history and record review, a Clinical Dementia Rating

(CDR) interview, the Functional Activities Questionnaire (FAQ), and a comprehensive neuropsychological assessment.

The SCD protocol and I-SCD protocol were identical to Aim 1 including the 25 item I-SCD, I-CCQ, and I-ECog.

The neuropsychological assessment protocol is comprised of a series of established measures of objective cognition that were selected to preclude ceiling or floor effects. This protocol measured global cognition, learning and memory, executive function, visuospatial ability, language, and information processing speed. The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) was used to measure global cognition. To measure memory and learning, a memory composite was derived from the California Verbal Learning Test-II Verbal List-Learning Task and the Biber Figure Learning Test Visual Learning Task. An executive functioning composite measure was derived from the Trail Making Task: Part B (TMT:B; set shifting), Delis-Kaplan Executive Function System: Color-Word Interference (inhibition), and the Tower Test (visual problem-solving). To measure visuospatial ability, the Hooper Visual Organization Task (HVOT) was used. Language was measured by a semantic fluency task (animal naming; naming as many animals as possible in one minute) and the Boston Naming Test (BNT) 30-item even version. The Wechsler Adult Intelligence Scale – 4th Edition (WAIS-IV) Coding task and the Trail Making Test: Part A (TMT:A) were used to measure processing speed. Participants completed the Geriatric Depression Scale (GDS; Yesavage et al., 1983) in order to assess depressed mood.

Biomarkers of the AD pathology, collected from lumbar puncture for CSF and brain MRI, include amyloid beta 42 ($A\beta_{42}$), total tau, phosphorylated tau (p-tau), and a brain MRI-derived AD signature (herein referred to as "AD signature"). All procedures were previously

detailed (Jefferson et al., 2016). Briefly, CSF was acquired through a morning fasting lumbar puncture with polypropylene syringes using a Sprotte 25-guage spinal needle in an intervertebral lumbar space. After samples were mixed and centrifuged, supernatants were aliquoted and stored at -80°C. Commercially available enzyme-linked immunosorbent assays (ELISA; Fujirebio, Ghent, Belgium) were used in batch to determine levels of Aβ42 (INNOTEST® β-AMYLOID$_{(1-42)}$) and total tau (INNOTEST® hTAU). Board certified laboratory technicians who were blinded to clinical information (Palmqvist et al., 2014) completed processing. Intra-assay CVs were <10%.

Brain MRI was completed at the Vanderbilt University Institute of Imaging Science using a 3T Phillips Achieva system (Best, The Netherlands) with an 8-channel SENSE receiver head coil. Regions of interest (ROIs) and intracranial volume (ICV) were calculated with T_1-weighted images (isotropic spatial resolution=1mm^3) using multi-atlas segmentation (Asman & Landman, 2012). Quantification of WMH was calculated using T_2-weighted fluid-attenuated inversion recovery (FLAIR) images (0.45x0.45x4mm^3) and post-processed using the Lesion Segmentation Tool toolbox for SPM8 (Schmidt et al., 2012).

Apolipoprotein-ε4 (*APOE*-ε4) carrier status was assessed through a fasting venous blood draw, previously detailed in Jefferson and colleagues' (2016) work, as previous literature has shown that positive carrier status is a genetic risk factor for developing AD (Kim et al., 2009). Plasma and serum were separated via centrifugation, and the remaining samples were stored at Vanderbilt at -80° C. Positive carrier status was defined by carrying at least one ε4 allele.

Table 3: Description for each VMAP measure

Measure	**Description**	**Direction (___ score indicates greater impairment)**

SCD score	45-item SCD questionnaire developed by Gifford and colleagues (2019) selected to determine the relationship between our derived I-SCD bank and a previously established SCD questionnaire	Higher
MoCA	Cognitive screener widely used in clinical and research settings to measure global cognition that has demonstrated utility in screening global cognition (Jefferson et al., 2016; Nasreddine et al., 2005) and relatively strong psychometric properties	Lower
Memory composite	Derived from metrics of the California Verbal Learning Test-II (verbal list-learning task) and the Biber Figure Learning Test (visual learning task)	Lower
Executive function composite	Derived from the following measures: Trail Making Task: Part B (cognitive flexibility and set-shifting), Delis-Kaplan Executive Function System: Color-Word Interference (inhibition)and Tower Test (visual problem-solving)	Lower
Hooper Visual Organization Task (HVOT)	Measures visual perceptual functioning and object recognition	Lower
Animal naming	Measures the ability to rapidly generate words from a semantic category (i.e., animals) in 60 seconds	Lower
Boston Naming Test (BNT) 30-item even version	Measures the ability to name pictures within 20 seconds of presentation (confrontational naming)	Lower
Wechsler Adult Intelligence Scale- 4th Edition (WAIS-IV) Coding	Measures the ability to decode symbols using a visual code	Lower
Trail Making Test: Part A (TMT:A)	Measures processing speed as the times needed to connect numbers in ascending order	Higher
Geriatric Depression Scale (GDS)	Assesses symptoms of depressed mood in older adults	Higher
$A\beta_{42}$	CSF biomarker that measures amyloidosis or amyloid deposition in the brain	Lower
Total Tau	CSF biomarker of neuronal damage	Higher
Phosphorylated-tau (p-tau)	CSF biomarker that measures neurofibrillary tangle burden in the brain	Higher
AD signature	Measures cortical thickness using brain MRI without contrast (Schwarz et al., 2016)	Lower
Apolipoprotein-ε4 (*APOE*-ε4) carrier status	Presence of *APOE*-ε4 gene assessed through blood sample Positive: ε2/ε4, ε3/ε4, ε4/ε4 Negative: ε2/ε2, ε2/ε3, ε3/ε3	n/a (positive or negative)
VMAP=Memory and Aging Project; SCD=subjective cognitive decline; I-SCD=informant-based subjective cognitive decline; MoCA=Montreal Cognitive Assessment; HVOT=Hooper Visual Organization Task; BNT=Boston Naming Test; WAIS-IV=Wechsler Adult Intelligence Scale- 4th Edition; TMT:A=Trail Making Test: Part A; GDS=Geriatric Depression Scale; $A\beta_{42}$=amyloid beta 42; AD signature=Alzheimer's disease signature; *APOE*-ε4= apolipoprotein-ε4; *p<0.05		

Statistical analyses

Descriptive statistics were calculated for all predictors (I-CCQ, I-ECog, Vanderbilt I-SCD, Vanderbilt I-SCD memory subdomain, Vanderbilt I-SCD executive function subdomain,

Vanderbilt I-SCD language subdomain, SCD score), all neuropsychological performances (MoCA, memory composite, executive function composite, HVOT, animal naming, BNT, WAIS-IV Coding, TMT A), CSF biomarkers of brain health ($A\beta_{42}$, total tau, p-tau), AD signature, participant demographics (age, sex, education, race/ethnicity), GDS score, and *APOE*-ε4 carrier status. Diagnosis (CU vs. CI) was based on a detailed diagnostic interview at screening visit. Descriptive statistics on informants included education, sex, and relation to the participant. Mann-Whitney U tests and Pearson's Chi-Square tests were used to calculate differences between groups.

To assess the utility of the Vanderbilt I-SCD as a diagnostic indicator, receiver operating characteristic (ROC) analyses assessed its sensitivity, specificity, and area under the curve (AUC) for diagnostic status. An optimal threshold (cutoff score) was chosen to maximize AUC. The sensitivity, specificity, and AUC for diagnostic status of the SCD measure were also assessed, and the DeLong test was used to compare AUC of the Vanderbilt I-SCD to AUC of the aforementioned SCD measure. Correlational analyses were used to determine the strength and direction of the relationships between the Vanderbilt I-SCD and each predictor. Then, Mann-Whitney U tests and Pearson's Chi-Square tests were used to compare Vanderbilt I-SCD score by participant sex, informant sex, and informant relation to participant. To assess the validity of the Vanderbilt I-SCD, logistic regressions related each Vanderbilt I-SCD total score to diagnosis and linear regressions associated each Vanderbilt I-SCD total to neuropsychological performances, GDS score, CSF variables, and AD brain signature in the entire sample. Regressions were repeated and stratified by diagnosis (CU vs. CI). All models were adjusted for age, sex, education, race/ethnicity, depressed mood, and *APOE*-ε4 carrier status.

All analyses were conducted using R statistical software.

RESULTS

Aim I: Development in IMASS

Participant characteristics

Five hundred thirty-seven participants met MASS inclusion criteria. Of these participants, 458 were CU and 79 were CI. In the entire sample, participants had an average age of 69 years (*SD:* 8 years) and had an average education of 16 years (*SD:* 2 years). Fifty-four percent of the total participants were female, and 95% of participants were non-Hispanic/White. The CU and CI participant groups were comparable for sex ($\chi_2(1) = 0.42$; $P = 0.52$) and race/ethnicity $\chi_2(1) = 0.01$; $P = 0.92$). CI participants were significantly older ($F(1,535) = 45.85$; $P < 0.001$), less educated ($F(1,535) = 9.77$; $P = 0.002$), had more depressed mood ($F(1,531) = 8.21$; $P = 0.004$) and greater SCD score ($F(1,532) = 9.33$; $P = 0.002$) than did the CI group. All results are summarized in **Table 4**.

Table 4: Characteristics of participants and informants (IMASS and MASS)

	Total (n=537)	**CU (n=458)**	**CI (n=79)**	***p*-value**	χ_2 **or F value**
Participant (MASS)					
Age, years	69±8	68±8	75±9	<0.001*	F(1,535) = 45.85
Education, years	16±2	16±2	15±3	0.002*	F(1,535) = 9.77
Sex, female	54%	55%	51%	0.52	$\chi_2(1) = 0.42$
Race/Ethnicity, non-Hispanic/White	95%	95%	95%	0.92	$\chi_2(1) = 0.01$
CESD Score	6±6	6±6	8±7	0.004*	F(1,531) = 8.21
SCD Total Score	62±22	61±21	68±23	0.002*	F(1,532) = 9.33
Informant (I-MASS)					
Age, years	62±13	62±13	63±13	0.90	F(1,526) = 0.02
Education, years	16±3	16±3	15±3	0.09	F(1,524) = 2.92
Sex, female	69%	68%	72%	0.45	$\chi_2(1) = 0.56$
Vanderbilt I-SCD, Total Score	57±27	53±23	75±37	<0.001*	F(1,509) = 21.46

MASS=Memory and Adults: A Survey Study; IMASS=Informant-based Memory and Adults: A Survey Study; CU=cognitively unimpaired; CI=cognitively impaired; CESD=Center for Epidemiological Studies Depression scale; SCD=subjective cognitive decline; Vanderbilt I-SCD=Vanderbilt Informant-based Subjective Cognitive Decline Questionnaire; *p<0.05

Informant characteristics

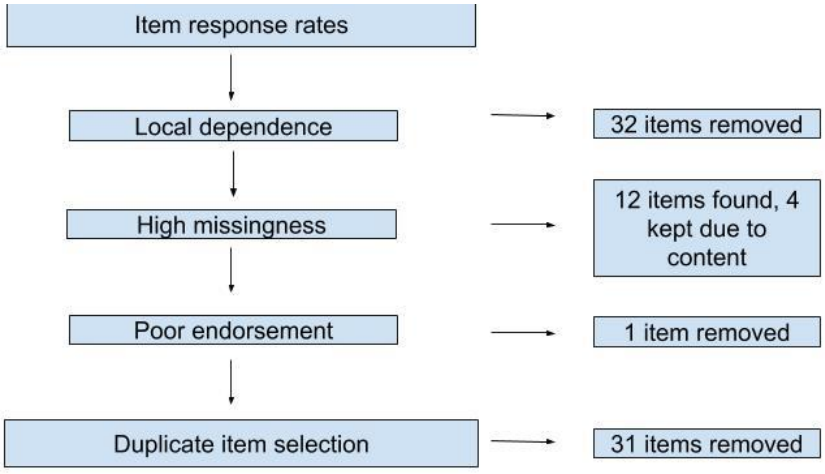
Informants had an average age of 62 years (*SD:* 13 years) and had an average education of 16 years (*SD:* 3 years). Sixty-nine percent of the informants were female, and their average score on the Vanderbilt I-SCD was 57 (*SD:* 27). The informants of the CU and CI participants were comparable in age ($F(1,526) = 0.02$; $P = 0.90$), sex $\chi_2(1) = 0.56$; $P = 0.45$), and education ($F(1,524) = 2.92$; $P = 0.09$). Informants of CI participants reported greater Vanderbilt I-SCD scores ($F(1,509) = 21.46$; $P < 0.001$) than did informants of CU participants.

Item Selection Process

Item response rates and duplicate selection

A flowchart of the item selection process, using items response rates and duplicate item removal, is presented in **Figure A**. Thirty-two items were removed due to local dependence. Twelve items showed high missingness, but four were kept due to content. One item was removed due to high proportion of a single response.

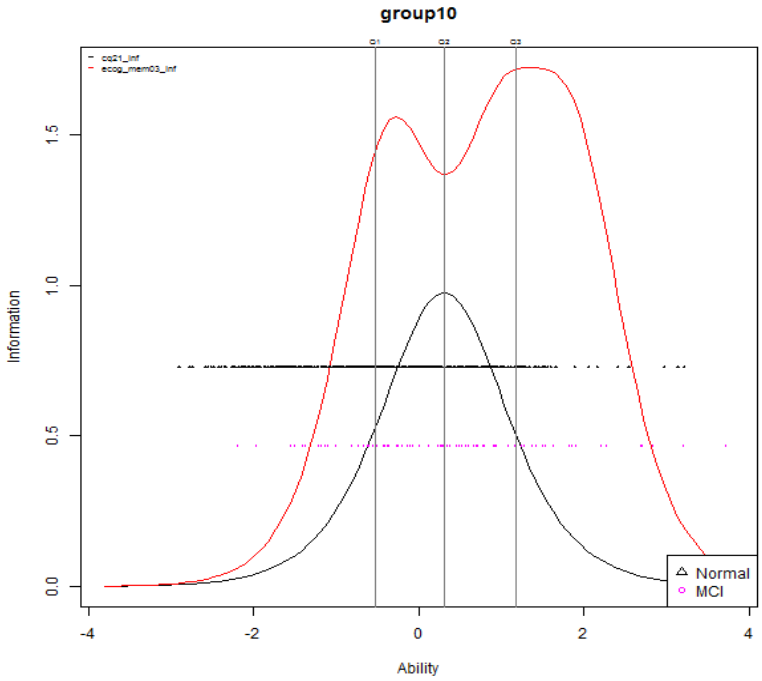
Figure A: Item selection flowchart for item response rates and duplicate selection



Manual review yielded 21 groups of items with similar content (e.g., attention, correspondence). Using item response theory, the most informative item(s) out of each group

was/were selected. Thirty-one items were removed at this step. **Figure B** shows an example item information curve.

Figure B: Item information curve example



Unidimensionality and factor analysis models

A flowchart of the item selection process using factor analysis is presented in **Figure C**. Factor analysis models were used to confirm unidimensionality of the trait and remove items with poor trait-fit. Unidimensionality of the latent trait was confirmed. An exploratory factor analysis on the remaining 30 items yielded an eigenvalue ratio of 7.67 between eigenvalue 1 (E1) and eigenvalue 2 (E2). One item was removed due to poor factor loading with the main factor. A confirmatory factor analysis one-factor model was fit to the remaining 29 items. Five items were removed due to better factor loading with individual factors than the group factors. A second EFA yielded an E1 to E2 ratio of 9.28 suggesting a strong general factor. In the second iteration

of CFA, two items that had better factor loading with individual factors than the group factor were removed. This analysis yielded a final list of 22 items.

Operationalized SCD criteria analyses

The final 22-item list from the factor analysis, as well as the items removed during this analysis, were examined for operationalized SCD criteria. Based on expert opinions, three items were added back in order for the questionnaire to meet all operationalized SCD criteria. These items include, “Do you think that the participant's memory is worse than 5 years ago?” “Do you have complaints about the participant's memory in the last 2 years?” and “Do you consider the participant's memory to be worse than others that are his/her same age?” The final 25-item bank is shown in **Table 5**.

Subdomain determination

The final 25 items were assigned to a subdomain of cognition based on a consensus of expert opinions. Of the final bank of items, 15 assess memory, four assess executive function, and six assess language. Items assigned to the subdomain of memory assessed the informant’s perception of the participant’s ability to recall information, past events, or conversations or asked the informant about changes in the participant’s memory over time. Executive function items assessed informant’s perception of the participant’s ability to complete multi-step tasks, maintain organization, and maintain attention to a task despite interruptions. Language items assessed informant’s perception of the participant’s ability to express himself or herself verbally, comprehend others’ speech, and find and remember the meaning of words.

Figure C: Item selection flowchart for factor analysis and operationalized SCD criteria analysis

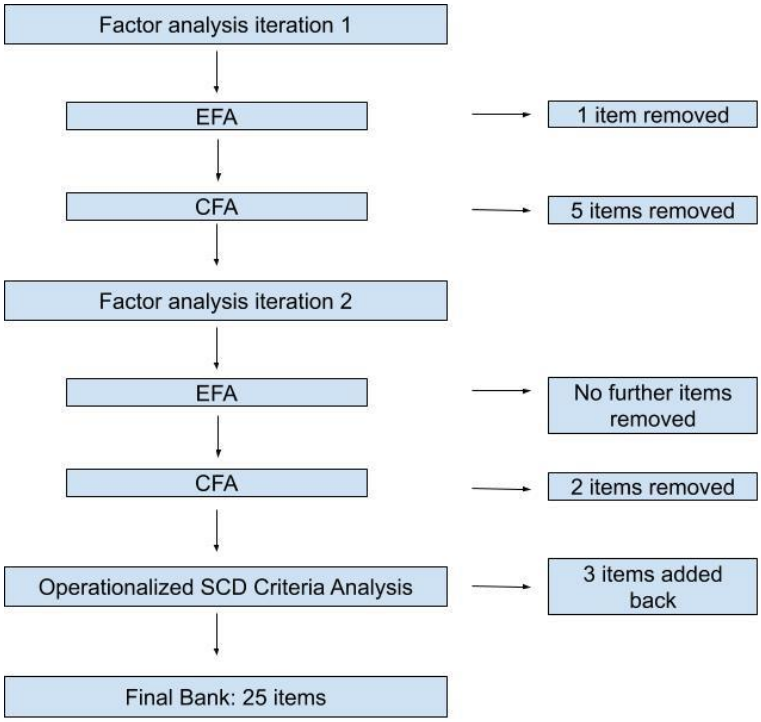


Table 5: Final 25-item bank

Item number	Question text	Subdomain	Original questionnaire	Discrimination	Difficulty
1*	Do you think that the participant's memory is worse than 5 years ago?	Memory	I-CCQ	-0.03	3.03
2*	Do you have complaints about the participant's memory in the last 2 years?	Memory	I-CCQ	1.73	2.49
3	Has the participant's memory changed significantly?	Memory	I-CCQ	4.21	3.36
4	Does the participant have difficulty with his/her memory?	Memory	I-CCQ	0.72	3.13
5*	Do you consider the participant's memory to be worse than others that are his/her same age?	Memory	I-CCQ	3.56	2.88
6	Do memory problems make it harder for the participant to complete tasks that used to be easy?	Memory	I-CCQ	3.17	2.88
7	Does the participant often have trouble finding the word he/she wants to use in everyday conversation?	Language	I-CCQ	2.60	2.47
8	Does the participant have trouble remembering things from one moment to the next?	Memory	I-CCQ	3.20	2.03

9	Returning to a task after being interrupted.	Executive Function	I-ECog	1.09	3.43
10	Verbally giving instructions to others.	Language	I-ECog	2.11	4.86
11	Communicating thoughts in a conversation.	Language	I-ECog	1.62	4.29
12	Remembering the meaning of common words.	Language	I-ECog	3.36	2.23
13	Describing a program he/she has watched on TV.	Language	I-ECog	2.65	4.98
14	Understanding spoken directions or instructions.	Language	I-ECog	1.68	4.10
15	Remembering a few shopping items without a list.	Memory	I-ECog	-0.52	2.48
16	Remembering things that happened recently (such as recent outings, events in the news).	Memory	I-ECog	1.08	4.01
17	Recalling conversations a few days later.	Memory	I-ECog	-0.19	3.43
18	Remembering where she/he has placed objects.	Memory	I-ECog	-1.10	1.98
19	Repeating stories and/or questions.	Memory	I-ECog	0.05	2.48
20	Remembering the current date or day of the week.	Memory	I-ECog	2.02	3.97
21	Remembering appointments, meetings, or engagements.	Memory	I-ECog	0.74	3.39
22	Keeping financial records organized.	Executive Function	I-ECog	1.99	3.61
23	Thinking things through before acting.	Executive Function	I-ECog	1.86	4.52
24	Following a map to find a new location.	Executive Function	I-ECog	1.23	3.10
25	Finding one's car in a parking lot.	Memory	I-ECog	1.35	3.91
I-CCQ=Cognitive Changes Questionnaire; I-ECog=Everyday Cognition Scale. *Item added back after factor analysis due to content.					

Aim II: Validation in VMAP

Participant characteristics

Participant characteristics for VMAP are summarized in **Table 6.** A total of 308 VMAP participants were included. Of these participants, 176 were CU and 132 were CI. In the entire sample, participants had an average age of 73 years (*SD:* 7 years), an average education of 16 years (*SD:* 3 years), and an average GDS score of 2 (*SD:* 3). Forty-two percent of the total

participants were female, and 87% of participants were Non-Hispanic/White. Thirty-five percent of participants in the total sample tested positive for *APOE*-ε4 carrier status.

The CU and CI participant groups were comparable for age ($F(1,306) = 0.54$; $P = 0.46$), sex ($\chi_2(1) = 0.28$; $P = 0.59$), and race/ethnicity ($\chi_2(1) = 0.23$; $P = 0.63$). CI participants had significantly less education ($F(1,306) = 20.26$; $P = 0.00$), had more depressed mood ($F(1,305) = 23.64$**;** $P = 0.00$), and were more likely to have positive *APOE*-ε4 carrier status ($\chi_2(1) = 7.39$) than the CU group.

On predictor measures, CI participants had significantly higher scores on the I-CCQ ($F(1,248) = 78.95$), I-ECog ($F(1,300) = 75.71$), Vanderbilt I-SCD ($F(1,226) = 82.75$), Vanderbilt I-SCD memory subdomain ($F(1,226) = 91.00$), Vanderbilt I-SCD executive function subdomain ($F(1,287) = 43.75$), Vanderbilt I-SCD language subdomain ($F(1,227) = 68.49$), and SCD score ($F(1,251) = 76.28$).

On neuropsychological assessment measures, CI participants had significantly lower scores on the MoCA ($F(1,305) = 153.05$; $P = 0.00$), memory composite ($F(1,305) = 243.55$; $P = 0.00$), executive function composite ($F(1,305) = 143.20$; $P = 0.00$), HVOT ($F(1,305) = 29.58$; $P = 0.00$), animal naming ($F(1,305) = 71.89$; $P = 0.00$), and BNT ($F(1,305) = 50.62$; $P = 0.00$), and WAIS-IV Coding ($F(1,305) = 64.94$). CI participants scored significantly higher on TMT:A ($F(1,305) = 54.00$).

On biomarker measures, CI participants showed significantly greater signs of AD, including lower levels of $A\beta_{42}$ ($F(1,138) = 11.80$; $P = 0.00$), higher levels of tau ($F(1,138) = 7.85$; $P = 0.01$), higher levels of phosphorylated tau ($F(1,138) = 4.47$; $P = 0.04$), and lower AD signature ($F(1,293) = 25.14$; $P = 0.00$).

Table 6: VMAP participant characteristics

	Total (n=308)	**CU (n=176)**	**CI (n=132)**	***p*-value**	**χ_2 or F value**

Age	72.912 (7.408)	72.568 (7.231)	73.371 (7.642)	0.46	F(1,306) = 0.54
Education	15.838 (2.659)	16.42 (2.455)	15.061 (2.729)	0.00*	F(1,306) = 20.26
Sex				0.59	$\chi_2(1) = 0.28$
Female	0.422 (130/308)	0.409 (72/176)	0.439 (58/132)		
Male	0.578 (178/308)	0.591 (104/176)	0.561 (74/132)		
Race/Ethnicity				0.63	$\chi_2(1) = 0.23$
Non-Hispanic White	0.867 (267/308)	0.875 (154/176)	0.856 (113/132)		
Other	0.133 (41/308)	0.125 (22/176)	0.144 (19/132)		
GDS Score	2.371 (2.876)	1.697 (2.263)	3.265 (3.334)	0.00*	F(1,305) = 23.64
APOE				0.01*	$\chi_2(1) = 7.39$
No	0.646 (199/308)	0.71 (125/176)	0.561 (74/132)		
Yes	0.354 (109/308)	0.29 (51/176)	0.439 (58/132)		
Predictors					
I-CCQ	34.265 (14.041)	28.257 (10.242)	42.7 (14.351)	0.00*	F(1,248) = 78.95
I-ECog	58.23 (18.212)	51.376 (12.485)	67.674 (20.541)	0.00*	F(1,300) = 75.71
Vanderbilt I-SCD score	25.982 (10.679)	21.266 (5.937)	32.705 (12.257)	0.00*	F(1,226) = 82.75
Vanderbilt I-SCD memory subdomain	14.257 (6.883)	11.103 (3.966)	18.754 (7.641)	0.00*	F(1,226) = 91.00
Vanderbilt I-SCD executive function subdomain	5.247 (2.171)	4.526 (1.249)	6.181 (2.697)	0.00*	F(1,287) = 43.75
Vanderbilt I-SCD language subdomain	6.545 (2.475)	5.598 (1.315)	7.88 (3.055)	0.00*	F(1,227) = 68.49
SCD score	62.198 (22.869)	52.937 (17.224)	75.251 (23.534)	0.00*	F(1,251) = 76.28
Outcomes					
MoCA	25.339 (3.389)	27 (2.231)	23.136 (3.413)	0.00*	F(1,305) = 153.05
Memory Composite	0 (0.978)	0.563 (0.718)	-0.746 (0.751)	0.00*	F(1,305) = 243.55
Executive Function Composite	-0.004 (0.918)	0.43 (0.609)	-0.581 (0.943)	0.00*	F(1,305) = 143.20
HVOT	24.404 (3.182)	25.303 (2.455)	23.212 (3.625)	0.00*	F(1,305) = 29.58
Animal Naming	18.902 (5.545)	20.954 (4.917)	16.182 (5.16)	0.00*	F(1,305) = 71.89
BNT	26.805 (3.196)	27.891 (2.01)	25.364 (3.851)	0.00*	F(1,305) = 50.62
WAIS-IV Coding	52.51 (12.96)	57.21 (11.6)	46.28 (12.05)	0.00*	F(1,305) = 64.94
TMT:A	42.46 (19.87)	35.97 (12.49)	51.06 (24.18)	0.00*	F(1,305) = 54.00
$A\beta_{42}$	703.379 (239.694)	760.048 (229.537)	620.86 (231.878)	0.00*	F(1,138) = 11.80
Tau	425.536 (234.857)	373.096 (173.676)	501.895 (287.63)	0.01*	F(1,138) = 7.85
P-Tau	60.793 (26.488)	56.145 (21.921)	67.561 (30.972)	0.04*	F(1,138) = 4.47
AD Schwarz Signature	2.305 (0.142)	2.34 (0.12)	2.256 (0.15)	0.00*	F(1,293) = 25.14

VMAP=Memory and Aging Project; CU=cognitively unimpaired; CI=cognitively impaired; GDS=Geriatric Depression Scale; APOE= apolipoprotein E4; I-CCQ=Cognitive Changes Questionnaire; I-ECog=Everyday Cognition; Vanderbilt I-SCD=Vanderbilt Informant-based Subjective Cognitive Decline Questionnaire; SCD=subjective cognitive decline; MoCA=Montreal Cognitive Assessment; HVOT=Hooper Visual Organization Task; BNT=Boston Naming Test; WAIS-IV=Wechsler Adult Intelligence Scale- 4th Edition; TMT:A=Trail Making Test: Part A; $A\beta_{42}$=amyloid beta 42; AD=Alzheimer's disease; *p<0.05

Informant characteristics

Informant characteristics for VMAP are summarized in **Table 7.** Two hundred twenty-eight VMAP participants in this study identified an informant. Informants had an average

education of 15 years (*SD:* 3 years). Seventy-four percent of the informants were female. Sixty-eight percent were a spouse/partner of a participant, 22% were an adult child, and 9% had another relation.

The informants of the CU and CI participant groups were comparable for education ($F(1,219) = 2.37$; $P = 0.13$) and sex ($\chi_2(1) = 0.68$; $P = 0.41$). There was a statistically significant difference in the types of informant relationship to the participant ($\chi_2(2) = 9.51$; $P = 0.01$).

Table 7. VMAP informant characteristics

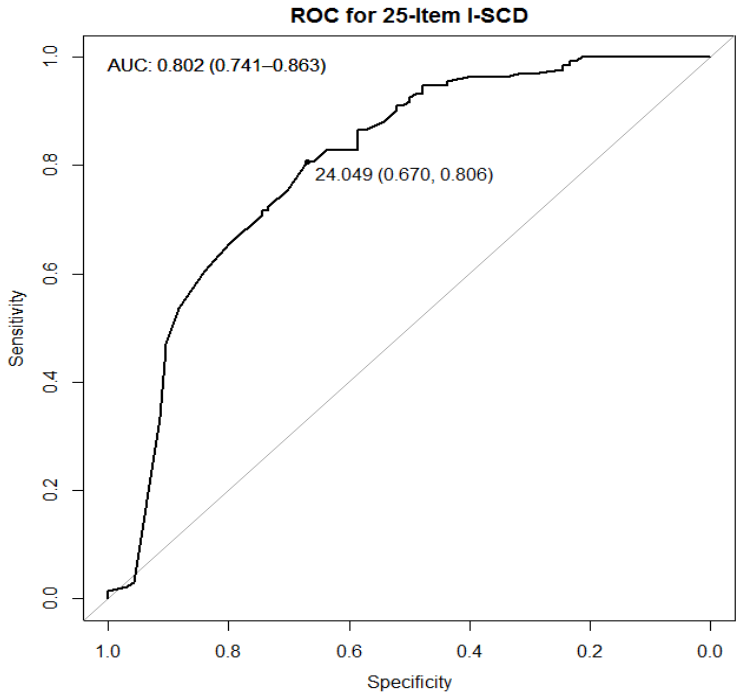
	Total (n=228)	**CU (n=134)**	**CI (n=94)**	***p*-value**	**χ_2 or F value**
Education	15.49 (02.55)	15.72 (2.39)	15.16 (2.73)	0.13	$F(1,219) = 2.37$
Sex				0.41	$\chi_2(1) = 0.68$
Female	0.74 (169/228)	0.76 (102/34)	0.71 (67/94)		
Male	0.26 (59/228)	0.24 (32/134)	0.29 (27/94)		
Informant Relation				0.01*	$\chi_2(2) = 9.51$
Spouse/Partner	0.68 (154/225)	0.62 (83/133)	0.77 (71/92)		
Adult Child	0.22 (50/225)	0.29 (39/133)	0.12 (11/92)		
Other	0.09 (21/225)	0.08 (11/133)	0.11 (10.92)		
VMAP=Memory and Aging Project; CU=cognitively unimpaired; CI=cognitively impaired; *p<0.05					

Receiver operating characteristic (ROC) analyses

The Vanderbilt I-SCD had a sensitivity of 0.81 and specificity of 0.67 at the optimal threshold of 24.05. This optimal threshold was chosen to maximize the area under the receiver operating characteristic curve (AUROC), which was 0.802 (95% CI: 0.74-0.86). The receiver operating curve for cognitive status is shown in **Figure D**. The sensitivity and specificity values for each threshold are presented in **Appendix A.**

For comparison, the 45-item SCD measure had a sensitivity of 0.63 and specificity of 0.80 at a threshold of 67 in this sample. It had an AUC of 0.783 (0.725-0.840) for predicting cognitive status. A comparison between the Vanderbilt I-SCD and SCD ROC curves resulted in a *p*-value of 0.65, indicating that there was not a statistically significant difference for predicting diagnosis in this sample.

Figure D: Receiver operating characteristic (ROC) curve for diagnosis



Correlational analyses

Correlations between the Vanderbilt I-SCD and other predictors, including I-CCQ, I-ECog, and the Vanderbilt I-SCD memory, language, and executive functioning subdomains, are shown in **Table 8**. In the entire sample, the Vanderbilt I-SCD showed a strong correlation with each of its parent measures, the I-CCQ (r = 0.88) and I-ECog (r = 0.96), as well as the memory subdomain (r = 0.98) and language subdomain (r = 0.82). The Vanderbilt I-SCD showed a strong correlation with the executive function subdomain (r = 0.79) and a moderate correlation with SCD score (r = 0.56). Correlations stratified by group show similar results, with a notable difference in executive function (CU r = 0.68; CI r = 0.89).

Table 8: Correlations between the Vanderbilt I-SCD and other predictors by group

	Vanderbilt I-SCD score	**I-CCQ**	**I-ECog**	**Vanderbilt I-SCD memory composite**	**Vanderbilt I-SCD executive function composite**	**Vanderbilt I-SCD language subdomain score**	**SCD (45 item participant score)**
Entire sample	**1**	0.88	0.96	0.98	0.79	0.82	0.56
CU	**1**	0.79	0.92	0.98	0.68	0.72	0.44
CI	**1**	0.87	0.97	0.98	0.89	0.85	0.31
Vanderbilt I-SCD=Vanderbilt Informant-based Subjective Cognitive Decline Questionnaire; I-CCQ=Cognitive Changes Questionnaire; I-ECog=Everyday Cognition; SCD=subjective cognitive decline; CU=cognitively unimpaired; CI=cognitively impaired							

Participant and informant sex and relation analyses

Comparisons of Vanderbilt I-SCD score by participant sex, informant sex, and informant relation are shown in **Tables 9-11.** There was no statistically significant difference in Vanderbilt I-SCD score by participant or informant sex. There was a statistically significant difference in Vanderbilt I-SCD score between the types of relationships between informant and participant, including spouse/partner, adult child, and other relationships ($P < 0.01$).

Table 9: Comparison of Vanderbilt I-SCD score by participant sex

	Female (n=130)	**Male (n=178)**	**Total (n=308)**	***p*-value**
Vanderbilt I-SCD	25.90 (10.81)	26.03 (10.64)	25.98 (10.68)	0.716
Vanderbilt I-SCD=Vanderbilt Informant-based Subjective Cognitive Decline Questionnaire				

Table 10: Comparison of Vanderbilt I-SCD score by informant sex

	Female (n=169)	**Male (n=59)**	**Total (n=228)**	***p*-value**
Vanderbilt I-SCD	25.96 (10.50)	26.04 (11.28)	25.98 (10.68)	0.658
Vanderbilt I-SCD=Vanderbilt Informant-based Subjective Cognitive Decline Questionnaire				

Table 11: Comparison of Vanderbilt I-SCD score by informant relation to participant

	Spouse/Partner (n=154)	**Adult Child (n=50)**	**Other (n=21)**	**Total (n=225)**	***p*-value**
Vanderbilt I-SCD	27.74 (11.32)	22.26 (7.40)	22.00 (9.38)	25.98 (10.68)	0.000*
Vanderbilt I-SCD=Vanderbilt Informant-based Subjective Cognitive Decline Questionnaire; *p<0.05					

Linear and logistic regression models

The results from linear and logistic regression models for both the CU and CI groups with Vanderbilt I-SCD as the predictor are presented in **Table 12.**

Greater Vanderbilt I-SCD score was significantly associated with greater likelihood of being in the CI group (OR= 1.14; 95% CI=1.10,1.20 ; $P < .000$) and greater SCD score (ß= 0.54; 95% CI= 0.28,0.79; $P = .000$).

On objective cognitive measures, greater I-SCD score was associated with lower scores on the MoCA (ß = -0.07; 95% CI= - 0.10, -0.04 ; $P = .000$), memory composite (ß = -0.02; 95% CI= -0.03, -0.01; $P = .000$), executive function composite (ß = -0.01; 95% CI= -0.02, 0.00 ; $P = .007$), and animal naming (ß = -0.08; 95% CI= -0.15, -0.02; $P = .012$). It was not significantly associated with HVOT, BNT, WAIS-IV Coding, or TMT:A. Vanderbilt I-SCD score was not significantly associated with GDS score.

On biomarker measures, greater Vanderbilt I-SCD score was significantly associated greater signs of AD markers, including lower levels of $A\beta_{42}$ (ß = -5.04; 95% CI= -9.25, -0.83; $P = .019$), higher levels of total tau (ß = 10.57; 95% CI= 6.73, 14.42; $P = .000$), higher levels of p-tau (ß = 1.09; 95% CI= 0.63, 1.56; $P = .000$), and smaller AD signature (ß = 0.00; 95% CI= 0.00, 0.00; $P = .008$).

Table 12: Linear and logistic regression model results for CU and CI participants with Vanderbilt I-SCD as the predictor

Outcome variable	**Estimate**	**Confidence interval**	***p*-value**
Diagnosis	1.14	(1.10, 1.20)	0.000*
SCD score	0.54	(0.28, 0.79)	0.000*
MoCA	-0.07	(-0.10, -0.04)	0.000*
Memory composite	-0.02	(-0.03, -0.01)	0.000*
Executive function composite	-0.01	(-0.02, 0.00)	0.007*
HVOT	-0.02	(-0.06, 0.02)	0.365
Animal naming	-0.08	(-0.15, -0.02)	0.012*
BNT	-0.03	(-0.07, 0.00)	0.073
WAIS-IV Coding	0.13	(-0.02, 0.28)	0.087
TMT:A	-0.05	(-0.29, 0.19)	0.666
GDS score	0.02	(-0.02, 0.06)	0.310
$A\beta_{42}$	-5.04	(-9.25, -0.83)	0.019*
Total tau	10.57	(6.73, 14.42)	0.000*

P-tau	1.09	(0.63, 1.56)	0.000*
AD signature	-0.002	(-0.004, -0.0006)	0.008*
CU=cognitively unimpaired; CI=cognitively impaired; Vanderbilt I-SCD=Vanderbilt Informant-based Subjective Cognitive Decline Questionnaire; SCD=subjective cognitive decline; MoCA=Montreal Cognitive Assessment; HVOT=Hooper Visual Organization Task; BNT=Boston Naming Test; WAIS-IV=Wechsler Adult Intelligence Scale- 4th Edition; TMT:A=Trail Making Test: Part A; GDS=Geriatric Depression Scale; $A\beta_{42}$=amyloid beta 42; AD signature=Alzheimer's disease signature; *p<0.05 Covariates: age, sex, education, race/ethnicity, GDS score, *APOE*-ε4 carrier status			

The results from linear and logistic regression models from the CU group only are presented in **Table 13.** Vanderbilt I-SCD score was only significantly associated with SCD score (ß = 0.59; 95% CI= 0.13, 1.05; *P* = 0.012).

Table 13: Linear and logistic regression model results for CU participants only with Vanderbilt I-SCD as the predictor

Outcome variable	**Estimate**	**Confidence interval**	***p*-value**
SCD score	0.59	(0.13, 1.05)	0.012*
MoCA	-0.04	(-0.09, 0.01)	0.136
Memory composite	-0.01	(-0.02, 0.01)	0.509
Executive function composite	-0.01	(-0.02, 0.01)	0.437
HVOT	0.01	(-0.05, 0.08)	0.658
Animal naming	0.07	(-0.06, 0.19)	0.308
BNT	0.01	(-0.05, 0.06)	0.854
WAIS-IV Coding	0.06	(-0.23, 0.35)	0.690
TMT:A	0.07	(-0.25, 0.39)	0.666
GDS score	0.03	(-0.04, 0.10)	0.391
$A\beta_{42}$	-3.13	(-12.69, 6.43)	0.515
Total tau	6.39	(-0.82, 13.60)	0.081
P-tau	0.57	(-0.31, 1.45)	0.199
AD signature	0.0004	(-0.002, 0.003)	0.797
CU=cognitively unimpaired; Vanderbilt I-SCD=Vanderbilt Informant-based Subjective Cognitive Decline Questionnaire; SCD=subjective cognitive decline; MoCA=Montreal Cognitive Assessment; HVOT=Hooper Visual Organization Task; BNT=Boston Naming Test; WAIS-IV=Wechsler Adult Intelligence Scale- 4th Edition; TMT:A=Trail Making Test: Part A; GDS=Geriatric Depression Scale; $A\beta_{42}$=amyloid beta 42; AD signature=Alzheimer's disease signature; *p<0.05 Covariates: age, sex, education, race/ethnicity, GDS score, *APOE*-ε4 carrier status			

Regression results from the CI group only are presented in **Table 14.** Greater Vanderbilt I-SCD score was significantly associated with higher SCD score (ß = 0.54; 95% CI= 0.19, 0.90; *P* = .003).

On objective cognitive measures, greater Vanderbilt I-SCD score was significantly associated with lower scores on the MoCA (ß = -0.09; 95% CI= 0.13, -0.04; $P < 0.01$), lower scores on memory tasks (ß = -0.02; 95% CI= -0.03, -0.01; $P < 0.01$), low scores on executive function tasks (ß = -0.02; 95% CI= -0.03, -0.00; $P = .020$), lower score on animal naming (ß = -0.13; 95% CI= -0.21, -0.05; $P = .002$), and higher score on WAIS-IV Coding (ß = 0.20; 95% CI= 0.01, 0.39; $P = .037$), indicating lower cognitive function. It was not significantly associated with HVOT, BNT, or TMT:A. Vanderbilt I-SCD score was not significantly associated with GDS score.

On biomarker measures, greater Vanderbilt I-SCD score was significantly associated with increased presence of AD biomarkers, including lower levels of $A\beta_{42}$ (ß = -7.45; 95% CI= -11.78, -3.13; $P = .001$), higher levels of total tau (ß = 11.10; 95% CI= 5.00, 17.2; $P = .001$), higher levels of p-tau (ß = 1.19; 95% CI= 0.46, 1.93; $P = .002$), and a lower AD signature (ß = -0.004; 95% CI= -0.006, -0.001; $P = .005$).

Table 14: Linear and logistic regression model results for CI participants only with Vanderbilt I-SCD as the predictor

Outcome variable	**Estimate**	**Confidence interval**	***p*-value**
SCD score	0.54	(0.19, 0.90)	0.003*
MoCA	-0.09	(-0.13, -0.04)	0.000*
Memory composite	-0.02	(-0.03, -0.01)	0.000*
Executive function composite	-0.02	(-0.03, -0.00)	0.020*
HVOT	-0.02	(-0.08, 0.03)	0.415
Animal naming	-0.13	(-0.21, -0.05)	0.002*
BNT	-0.04	(-0.10, 0.01)	0.117
WAIS-IV Coding	0.20	(0.01, 0.39)	0.037*
TMT:A	-0.15	(-0.53, 0.24)	0.450
GDS score	0.02	(-0.03, 0.06)	0.522
$A\beta_{42}$	-7.45	(-11.78, -3.13)	0.001*
Total tau	11.10	(5.00, 17.2)	0.001*
P-tau	1.19	(0.46, 1.93)	0.002*
AD signature	-0.004	(-0.006, -0.001)	0.005*

CI=cognitively impaired; Vanderbilt I-SCD=Vanderbilt Informant-based Subjective Cognitive Decline Questionnaire; SCD=subjective cognitive decline; MoCA=Montreal Cognitive Assessment; HVOT=Hooper Visual Organization Task; BNT=Boston Naming Test; WAIS-IV=Wechsler Adult Intelligence Scale- 4th Edition; TMT:A=Trail Making Test: Part A; GDS=Geriatric Depression Scale; $A\beta_{42}$=amyloid beta 42; AD signature=Alzheimer's disease signature; *p<0.05

Covariates: age, sex, education, race/ethnicity, GDS score, *APOE*-ε4 carrier status

DISCUSSION

The goal of the present study was to develop and validate an informant-based subjective cognitive decline measure, the Vanderbilt I-SCD, to detect unhealthy brain aging in adults. The Vanderbilt I-SCD included 25 items and fulfilled all operationalized SCD criteria. Within the validation cohort, the total score of the Vanderbilt I-SCD significantly discriminated between CU and CI. Total Vanderbilt I-SCD score was significantly associated with self-SCD, objective cognitive measures, and biomarkers associated with unhealthy brain aging, with strongest associations noted within the CI group.

Aim 1: Development in IMASS

Results supported the feasibility of using latent variable modeling to identify reliable I-SCD items. Unidimensionality was confirmed via CFA, indicating that the questionnaire measures one latent variable (i.e., I-SCD). The fact that we found one dimension is slightly different from that of previous works with a similar purpose of using latent variable modeling to derive an I-SCD questionnaire (Sikkes et al., 2011; Tomaszewski Farias et al., 2008). However, Sikkes and colleagues (2011) showed the two factors of their two-dimensional model were highly correlated, and Tomaszewski Farias and colleagues (2008) were not looking for unidimensionality. Other works, such as the development of the 12-item, informant-based ECog Short Form (Tomaszewski Farias et al., 2011) and Cognitive Change Checklist (Schinka et al., 2009) found unidimensionality. Lastly, the final bank met all operationalized SCD criteria (Jessen, Amariglio, et al., 2014), as these criteria have been shown to increase the likelihood that

an individual has preclinical AD when used for self-report measures (Jessen, Amariglio, et al., 2014).

Aim II: Validation in VMAP

After identifying items for the Vanderbilt I-SCD, the tool was compared to other markers of unhealthy brain aging in an independent cohort (VMAP). Comparisons of Vanderbilt I-SCD score by sex did not yield any significant differences for either participant sex or informant sex. Comparisons of Vanderbilt I-SCD score by type of informant relationship (spouse/partner, adult child, or other) revealed a significant difference between types of informant. Spouses/partners tended to rate their loved one as having greater cognitive decline than adult children or other informants.

I-SCD & Cognition

In the entire VMAP cohort (CU and CI participants), greater Vanderbilt I-SCD score was significantly associated with lower cognitive performance on measures of global cognition, memory, and executive function, as well as inconsistently associated with measures of language. These significant relationships suggest that the questionnaire is able to pick up on subdomains of the participant's cognition, including memory, executive function, and language, domains that are readily assessed among existing I-SCD measures (Rami et al., 2014; Rattanabannakit et al., 2016). The prominence of these subdomains is not surprising given their relevance to the AD pathology and its clinical manifestation. Neuropathological changes characteristic of presumptive AD, including amyloidosis and tau deposition, begin in the hippocampus, resulting in the clinical manifestation of memory loss (Dubois et al., 2016; Jahn, 2013). As AD pathology progresses, deterioration has been shown in temporal and frontal lobe regions, affecting language

and executive function respectively, as well as in parietal lobe regions (McDonald et al., 2009; Wenk, 2003).

In the whole sample analyses, Vanderbilt I-SCD score was not significantly associated with HVOT, WAIS-IV Coding, TMT:A, or BNT. Lack of association with processing speed and visuospatial skills, required in HVOT, WAIS-IV Coding, and TMT:A, could suggest that the Vanderbilt I-SCD does not capture all aspects of cognition. However, it is important to note that visual processing was only addressed in two questions ("Following a map to find a new location" and "Finding one's car in a parking lot"), showing the relative lack of prominence of this subdomain in the questionnaire. The lack of a significant association with the BNT is surprising given the significant association between the Vanderbilt I-SCD and the other language measure, animal naming. This result was inconsistent with a previous study by Russo and colleagues (2018), which found a significant negative correlation between the BNT and Spanish version of the I-ECog in a cohort comprised of cognitively normal, MCI, and mild AD subjects. Possible explanations for this difference include the use of a different measure (selected questions from the I-ECog and I-CCQ in the present study instead of the full I-ECog), the use of a different version of the I-ECog, and the inclusion of mild AD in the cohort from the previous study.

Regressions stratified by group show that the CI group is driving the significant associations seen across the entire sample. All significant associations between Vanderbilt I-SCD and objective measures of cognition found in the entire sample were consistent in the CI group, whereby higher Vanderbilt I-SCD was related to lower cognition. In addition, WAIS-IV Coding had a significant positive association in the CI group only, suggesting that as Vanderbilt I-SCD increases, CI participants' processing speed is slower. Although the relationship between Vanderbilt I-SCD and WAIS-IV Coding was not significant in the entire sample (CU+CI), both

the magnitude and strength of the relationship were close to those significant values in the stratified CI analysis. Considering these results cumulatively, the Vanderbilt I-SCD questionnaire shows best utility in the prodromal stage (MCI) of dementia due to presumable AD.

Furthermore, Vanderbilt I-SCD was not significantly associated with participant GDS score in any of the linear regression models. This finding supports previous studies that I-SCD is not subject to the same influence of depression as self-reported SCD (Grut et al., 1993; Rabin et al., 2017).

I-SCD & AD Biomarkers

Greater Vanderbilt I-SCD scores were associated with increased amyloidosis (as measured by a decrease in CSF Aβ42), increased neurodegeneration (total tau), increased neurofibrillary tangles (p-tau), and lower AD signature. These associations were driven by the CI group, indicating that the Vanderbilt I-SCD is better at determining AD pathology in the prodromal stage. These findings are somewhat consistent with previous research examining the association between Vanderbilt I-SCD and biomarkers of AD pathology. In a cross-sectional sample using the SCD-Q to measure I-SCD, Valech and colleagues (2015) found that I-SCD is associated with amyloidosis and tau deposition (tau and p-tau) in individuals with cognitive impairment. In a cross-sectional sample of a longitudinal study using the IQCODE to assess I-SCD, Dong and colleagues (2018) found no significant difference in cortical thickness between individuals with informant-reported cognitive decline and individuals with normal cognition. This difference in results may be attributed to the different measures used for assessing I-SCD (Vanderbilt I-SCD vs. IQCODE).

I-SCD & Diagnostic Status

As predicted, the Vanderbilt I-SCD successfully discriminated between CU and CI subjects (AUC > 0.8) at a cutoff score of 24, meaning its results align with diagnostic group classification for greater than 80% of participants. Given the substantial differences between Vanderbilt I-SCD scores that is dependent on diagnostic status, we believe the Vanderbilt I-SCD is a valid indicator of cognitive status and AD pathology based on the present study. Overall, this finding aligns with previous literature supporting the validity of I-SCD (e.g., Archer et al., 2007; Caselli et al., 2013; Edmonds et al., 2014; Fyock & Hampstead, 2015).

I-SCD & SCD

The Vanderbilt I-SCD had a moderately strong correlation with SCD score, measured by a previously developed 45-item self-report questionnaire (Gifford et al., 2019) in the entire sample. The correlation was weaker than that of the entire sample in the CU group, and even weaker in the CI group. This finding suggests that agreement between self and informant decreases as cognitive decline increases. Although discrepancy between self and informant scores on the same measure was not directly assessed in the present study, a decrease in agreement can be viewed as analogous to an increase in discrepancy. Previous cross-sectional and longitudinal studies on self vs. informant discrepancy scores suggest that discrepancy generally increases as cognitive decline increases and patients likely develop anosognosia (Rattanabannakit et al., 2016; Silva et al., 2016). This increase is not necessarily linear, as the complex relationship between self and informant report in the preclinical stage may lead to an interaction between cognitive decline and discrepancy (Bregman et al., 2020; Edmonds et al., 2014).

There was a significant positive association across linear and logistic regression analyses (CU + CI, CU only, and CI only) between Vanderbilt I-SCD and SCD, supporting the positive

correlation found between these two variables in all correlational analyses. Interestingly, this association was the only significant association in the stratified linear and logistic regression results for the CU group, indicating agreement between the self and informant in the absence of cognitive impairment. These findings support a previous study by Buckley and colleagues (2015), which found that self and informant report align in the early stages of MCI. On the other hand, given the complex relationship between self and informant in the absence of objective cognitive impairment found in previous literature (Bregman et al., 2020; Edmonds et al., 2014), this finding is somewhat surprising because some individuals report cognitive impairment subjectively in the absence of cognitive impairment on objective measures. This relative level of agreement may not have accounted for higher self-concern in some participants.

Vanderbilt I-SCD had a slightly higher AUC for discriminating between CU and CI than the 45-item SCD, but this difference was not statistically significant. Although discrepancy between self- and informant-report score on the same measure was not directly addressed in this study, the moderate correlation between these measures indicated that informants and participants sometimes differed in their report. The presence of a difference between self and informant scores is consistent with previous discrepancy studies (Cacciamani et al., 2017; Edmonds et al., 2018; Gifford et al., 2014; Miller et al., 2013; Sundermann et al., 2018), as SCD has been shown to be more predictive in the preclinical stage (Jessen, 2014; Studart & Nitrini, 2016; Mendonca et al., 2016; Rabin et al., 2017) and I-SCD has been shown to be more predictive in the prodromal stage (Buelow et al., 2014; Gifford et al., 2014; Rabin et al., 2017; Rattanabannakit et al., 2016).

General discussion

Our findings are especially relevant considering the importance of early detection; its role in management, treatment, and reducing healthcare costs; and the current emphasis on defining the best methodology for evaluating SCD. In conjunction with SCD endorsements, our questionnaire may help distinguish between the "worried well" and those with the early clinical signs of unhealthy brain aging in the prodromal stage of AD.

The Vanderbilt I-SCD was developed using the operationalized SCD criteria because these criteria, when used for self-report, have been shown to increase the likelihood that an individual has preclinical AD (Jessen, Amariglio, et al., 2014). The inclusion of the SCD-plus criteria in a recent semi-structured interview that is primarily based on self-report (SCD-I; Miebach et al., 2019) further supports the utility of these criteria in SCD questionnaire development. However, there are no current informant-based SCD questionnaires or structured interviews that meet these criteria. The development of our questionnaire was based on the assumption that these operationalized SCD criteria will be valid when applied to an informant-based measures. Our findings indicate that although the inclusion of these criteria did not result in strong validity of I-SCD in the preclinical stage, our questionnaire showed strong validity with cognitive status and AD pathology in the prodromal stage. Therefore, the inclusion of these criteria in I-SCD questionnaires in future research is supported.

Clinically, this questionnaire may eventually be used as a key measure in determining cognitive status once early cognitive symptoms have been reported, after more validation research (to be discussed) has been conducted. In the present study, the questionnaire has shown strong validity as a marker of cognitive status and AD pathology in the prodromal stage. Given its utility in determining cognitive status, its use as an evaluation instrument may mitigate the need for complex follow-up through objective neuropsychological assessment. While our

analyses looked at the Vanderbilt I-SCD as a continuous measure, it has the opportunity to have a cutoff score, thus enabling its use as a screening measure. After further research, it may eventually be used as a screening measure by primary care providers or clinicians with a background in cognition (e.g., speech-language pathologists, or occupational therapists) to screen for the need for complex cognitive follow-up. When used for screening purposes, it should be combined with a self-report SCD measure so that both SCD in the preclinical stage and I-SCD in the prodromal stage can be detected.

Furthermore, it may be used as one of several qualitative instruments in cognitive-communication evaluations by speech-language pathologists to inform treatment. Although previous literature has suggested that I-SCD should not be used to differentiate between deficits in subdomains of cognition (Abbate et al., 2011), having a relative or other informant of the patient complete the Vanderbilt I-SCD could provide valuable information to speech-language pathologists about a patient's cognitive status and potential areas of treatment, especially when combined with a self-report measure. Speech-language pathologists may use it as a starting point for a clinical interview with the patient and informant or, in part, to inform a clinical decision between objective cognitive measures to use during an evaluation. They may also use it for periodic progress monitoring during cognitive treatment/management, as a notable increase in score may indicate the need for further evaluation by a neuropsychologist or physician.

This work is not without some limitations. For example, the questionnaire shares some of the limitations discussed with other I-SCD measures. First, similarly to the CCI (Rattanabannakit et al., 2016), DECO (Ramlall et al., 2013), and SIRQD (Yim et al., 2017), it has not yet been studied longitudinally. Second, it is possible that there were spurious findings in the validation results given multiple analyses. Third, the cohorts in the present study were highly

educated and largely homogenous in race/ethnicity, so the results may not generalize to individuals with less education or individuals of other races/ethnicities. Fourth, it may be influenced by informant mood, as previous literature has suggested this may be a confounding variable (Jorm et al., 2004; Mograbi et al., 2015) that was not addressed in the present study.

Directions of future research will focus on expanded validation of the Vanderbilt I-SCD by using longitudinal study design in a cohort that includes subjects with normal cognition, MCI, and AD. In addition, discrepancy between self- and informant-SCD will be examined. Specifically, we will examine underreporting and overreporting in both the preclinical and prodromal stages. We will also examine mutual complaint and determine which cutoff scores are most appropriate to define mutual complaint in the present measure. Furthermore, the inclusion of all operationalized SCD criteria (Jessen, Amariglio, et al., 2014) in our questionnaire suggests that these criteria may have utility pertaining to informant report in the prodromal stage. Therefore, the inclusion of these criteria in future I-SCD questionnaires is indicated.

In summary, we developed the 25-item Vanderbilt I-SCD Questionnaire from the I-ECog and I-CCQ that meets all operationalized SCD criteria (Jessen, Amariglio, et al., 2014). When validated cross-sectionally in an independent cohort, the questionnaire showed strong validity compared with objective measures of cognition, biomarkers associated with the AD pathology, and a previously developed measure of SCD (Gifford et al., 2019). It significantly discriminated between CU and CI participants. With more research, this Vanderbilt I-SCD could eventually be used clinically as a time-effective evaluation tool or as a screener for cognitive impairment associated with unhealthy brain aging.

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APPENDIX

Appendix A: Full ROC results at each threshold for Vanderbilt I-SCD measure

Threshold	Sensitivity	Specificity
15.500	0.968	0.022
16.500	0.957	0.030
17.500	0.915	0.336
18.007	0.904	0.463
18.507	0.904	0.470
19.500	0.883	0.537
20.500	0.840	0.604
21.500	0.798	0.657
22.035	0.745	0.709
22.083	0.745	0.716
22.309	0.734	0.716
22.761	0.734	0.724
23.500	0.702	0.754
24.049*	0.670	0.806
24.549	0.660	0.806
25.111	0.638	0.828
25.611	0.628	0.828
26.188	0.596	0.828
26.688	0.585	0.828
27.139	0.585	0.866
27.639	0.574	0.866
28.500	0.543	0.881
29.111	0.521	0.903
29.444	0.521	0.910
29.833	0.511	0.910
30.146	0.500	0.918
30.646	0.500	0.925
31.318	0.489	0.933
31.652	0.479	0.933
31.833	0.479	0.940
32.500	0.479	0.948
33.153	0.436	0.948
33.653	0.436	0.955
34.045	0.404	0.963
34.545	0.394	0.963
35.500	0.372	0.963
36.500	0.340	0.963
37.222	0.319	0.970
38.222	0.309	0.970
40.000	0.298	0.970
41.729	0.245	0.978
42.486	0.245	0.985
42.779	0.234	0.985
43.522	0.234	0.993
44.500	0.223	0.993

ROC=Receiver operating characteristic; I-SCD=Informant-based subjective cognitive decline
*Threshold value chosen as optimal cutoff