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Comparing Patient and Informant Ratings of Depressive Symptoms in Various Stages of Alzheimer's Disease

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Abstract

Objective: Using a multimethod approach, this study assessed the relationship between patient and informant ratings of depression in Alzheimer's disease (AD) in a manner that better represents the progressive course of AD, and allows for elucidation of specific cognitive domains which may explain changes in respondent agreement.

Method: Case data (N=16,297) were provided by the National Alzheimer's Coordinating Center (NACC). A series of contingency analyses were performed to assess the relationship between patient and informant agreement across levels of impairment in individuals with AD. Patients and informants were placed into groups (i.e., not impaired, mild impairment, moderate impairment, severe impairment) based on patients' performance on multiple indicators of global cognitive functioning, as well as measures of attention, working memory, processing speed, executive functioning, language, and episodic learning and memory.

Results: Across measures, greater impairment was significantly (p<0.001) associated with decreases in patient-informant congruence and increases in rates of patients denying depression when informants endorsed observing features of the same. These inconsistencies were most pronounced in the mildest stages of impairment. For a subset of the sample, rates of patients reporting depressive symptoms when informants denied observing the same also increased alongside worsening impairment. Incremental impairment in episodic learning (χ^2 = 805.25) and memory (χ^2 = 856.94) performance were most closely associated with decreases in respondent agreement. Patient-informant relationship type did not appear to mediate the response patterns observed.

Conclusions: Mild impairment in AD patients, particularly in episodic learning and memory functioning, is significantly associated with decreases in patient-informant agreement regarding the presence of depressive symptoms. These results suggest that even at the earliest stages of AD informant reports should be used to corroborate patients' reporting.

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This study was part of Dov Gold's doctoral dissertation, done under the supervision of Samuel Justin Sinclair, Department of Clinical Psychology, William James College. The full dissertation will be hosted in ProQuest following an embargo period.

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Keywords

Alzheimer's Disease; Dementia; Mild Cognitive Impairment; Anosognosia; Neuropsychiatry

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, and is estimated to account for around 60-70% of the nearly 50 million dementia diagnoses worldwide (World Health Organization, 2017; Yang et al., 2017). In the United States, AD is the sixth leading cause of death, affecting over five million Americans (Alzheimer's Association, 2017). The prevalence rate of the disease is expected to steadily rise as members of the baby boom generation continue to enter older-adulthood. The disease currently has no cure.

In patients with dementia, at least one neuropsychiatric symptom (i.e., changes in mood, perception, or behavior) is likely to occur over the course of the disease, with some studies estimating symptoms in as high a 80% of cases (Lyketsos et al., 2002). Depressive symptoms are among the most common neuropsychiatric symptoms and occur in up to 50% of all cases (Modrego, 2010). Symptoms of depression have widely been associated with worse performance in multiple areas of cognitive functioning. (Blazer, 2003; Brewster, Peterson, Roker, Ellis, & Edwards, 2017; de Paula et al., 2016; Sexton et al., 2012; Shimada et al., 2014). For example, a recent meta-analysis revealed a significant negative correlation between severity of depressive symptoms and performance on neuropsychological measures of speed and executive functioning (i.e., greater depressive symptoms leads to worse performance) (McDermott & Ebmeier, 2009). Likewise, in a recent review of existing literature on depression in older adults, Sivertsen, Bjørkløf, Engedal, Selbæk, & Helvik (2015) reported that greater levels of depression were consistently associated with poorer quality of life in older adults.

Interaction Between Depression and Alzheimer's

Considering the cognitive and functional impacts of depressive symptoms in neurologically healthy adults (Wang & Blazer, 2015), it is unsurprising that symptoms of depression in patients with AD have been associated with greater global cognitive impairment and poorer performance on measures of complex attention, working memory, speed, and episodic memory (Christensen, Griffiths, Mackinnon, & Jacomb, 1997; Espiritu et al., 2001; Nakaaki et al., 2007; Yatawara, Lim, Chander, Zhou, & Kandiah, 2016). There is also evidence linking depressive symptoms in AD with a greater functional impairment in activities of daily living and poorer quality of life than AD alone (Fitz & Teri, 1994; Lyketsos et al., 1997; Pearson et al., 1989; Potter & Steffens, 2007).

In addition to more severe impairments, research suggests that symptoms of depression in AD patients are associated with an increased rate of decline over time (Butters et al., 2008; Byers & Yaffe, 2011; Jorm, 2001; Van der Mussele et al., 2014; Wilson et al., 2014; Yang et al., 2017). In one longitudinal study where 183 patients with mild cognitive impairment were evaluated for depression at baseline, significant symptoms of depression appeared to be linked with an increased risk of later conversion to dementia due to AD. (Van der Mussele et

al., 2014). Wilson and colleagues (2014) offered further support for this association utilizing data from two large cohort studies, which included cognitive assessment data, measures of depression, and results from postmortem neuropathologic examinations. Their findings indicated that the incidence of both mild cognitive impairment and dementia were associated with a higher level of depressive symptoms before their respective onset. They also found that levels of depression over time were independent of neuropathologic disease burden, and when controlling for neurological markers of 6 types of dementia-related pathology, higher levels of depression were associated with an increased rate of cognitive decline (Wilson et al., 2014). In further support of this relationship, Karavasilis and colleagues (2017) demonstrated patients with AD and depression display patterns of grey matter atrophy distinct from changes typically seen in AD alone, characterized by more extensive reductions in grey matter volume in sensory and motor areas, as well as the right thalamus.

Challenges in Identifying Depression in Alzheimer's Patients

Considering the high comorbidity as well as the cognitive and functional consequences of depressive symptoms in AD, it is critical for clinicians to be able to accurately detect, and subsequently treat and manage symptoms of depression in AD patients. In fact, treatments comprising cognitive-behavioral interventions or psychopharmacological medication have been shown to contribute to significant and lasting reductions in depressive symptoms and corresponding improvements in activities of daily living (Lyketsos et al., 2003; Sink, Holden, & Yaffe, 2005; Teri & Gallagher-Thompson, 1991; Teri, Logsdon, Uomoto, & McCurry, 1997). Brief self-report questionnaires are commonly used to detect depression, as they typically correlate well with clinician ratings and require significantly less time and clinical resources to administer and interpret (Katzelnick et al., 2011; Uher et al., 2012; Zimmerman, Walsh, Friedman, Boerescu, & Attiullah, 2018). Self-report measures for specific age groups exist as well, including the Geriatric Depression Scale (GDS; Shiekh & Yesavage, 1986; Wancata, Alexandrowicz, Marquart, Weiss, & Friedrich, 2006; Yesavage et al., 1982), which was designed to significantly reduce the emphasis of physical symptoms when screening for symptoms of depression among older adult populations.

Despite the utility and convenience of using self-report measures to assess for symptoms of depression in cognitively normal adults, there are important considerations when using these tools to detect depression in patients with AD that may limit their utility with this population. As mentioned, AD typically presents as a progressive memory disorder that initially impacts one's ability to encode new information for later retrieval, and eventually results in the loss of information stored in long-term memory (Blumenfeld, 2010; Sperling et al., 2010; Weintraub et al., 2012; Zillmer et al., 2007). As a consequence of widespread neurodegeneration, the insight that AD patients may have regarding their symptoms and difficulties in daily life inevitably becomes compromised (Frank, Lenderking, Howard, & Cantillon, 2011; Snow et al., 2005). This loss of insight, 'anosognosia,' can be observed to varying degrees in nearly half of the patients in the early stages of AD, and increases in occurrence and severity as AD progresses (Oba et al., 2018; Orfei et al., 2010; Verhülsdonk, Quack, Höft, Lange-Asschenfeldt, & Supprian, 2013).

Anosognosia in AD patients is extremely important when it comes to using self-report measures to screen for and quantify symptoms of depression, as it has been linked to inaccuracies in reporting where patients may underreport or completely deny the presence of depressive (or other affective) symptoms (Burke et al., 1989; Frank et al., 2011; Verhülsdonk et al., 2013). For example, in one study where cognitive impairment was determined using the Clinical Dementia Rating scale (CDR® Dementia Staging Instrument), the sensitivity of the of the GDS dropped to 0.25 for patients with CDR® scores in the mildly impaired range and above (Montorio & Izal, 1996). Similarly, Gilley & Wilson, (1997) reported that the presence of Alzheimer's dementia as indicated by the Mini-Mental State Examination (MMSE) significantly increased the rate of false negatives on the GDS. This is even more concerning when considering that most studies rely on self-report data to evaluate depression severity in AD patients. That said, some have suggested that the effects of anosognosia are only an issue for respondents in the more moderate to severe stages of AD (Burke, Nitcher, Roccaforte, & Wengel, 1992; Feher, Larrabee, & Crook, 1992). Given these mixed findings, more research is needed into the anosognosia phenomenon before best practices for using self-reports with AD patients can be established and implemented.

The use of informants (e.g., family members, friends, and caregivers) may offer a potential solution to this problem; this information can help corroborate patients' reporting, assess for symptoms not observed in the clinical settings, and in the case of patients with AD, characterize patients' functioning in ways that are less subject to the influence of worsening cognitive symptoms (Frank et al., 2011; Wang & Blazer, 2015). That said, informant-reports pose their own risk of error as well. Verhülsdonk and colleagues (2013) described that the use informant-report measures in AD risks exaggerating the reality due to the burden of AD caregivers. Others have also commented on this possibility (Cacchione, Powlishta, Grant, Buckles, & Morris, 2003; Frank et al., 2011; Rabin et al., 2017), and one study found filial burden significantly contributed to the discrepancies observed between informant-rated and self-rated levels of depression in AD patients (Burke et al., 1998). Other factors have been shown to influence the accuracy of informant-reports as well, including informant personality factors, the nature of patient-respondent relationships, and the frequency and intensity of interactions between AD patients and informants (Brown & Schinka, 2005; Cacchione et al., 2003; Rabin et al., 2017).

Comparing Methods of Identification

Research directly evaluating discrepancies regarding the presence of depressive symptoms in patients with AD has provided mixed results (Burke et al., 1998; Carvalho, Tan, Springate, & Davis, 2013; Müller-Thomsen et al., 2005; Snow et al., 2005; Verhülsdonk et al., 2013), though studies often report large discrepancies between patients, clinicians, and informants in terms of the level of depression reported, particularly at the later stages of the AD process. For instance, Burke and others (1998) compared self-reported levels of depression in patients diagnosed with probable AD to ratings from caregivers. Their findings demonstrated a statistically significant discrepancy in the level of depressive symptoms reported by those with AD and their informants. Furthermore, Burke and colleagues (1998) found that the magnitude of the discrepancy among AD patients and their informants was significantly greater than that of the controls (Burke et al., 1998). Others have identified discrepancies

when comparing patient and informant reports as well, and have argued that patients' insight into their symptoms may independently attenuate patterns of agreement, even when other cognitive abilities are relatively intact (Ott and Fogel, 1992; Snow et al., 2005)

That said, some older studies have argued that patients' self-reported symptoms of depression correlate well with the others' perspectives. For instance, in a group of individuals with mild to moderate dementia, O'Riordan and others (1990) found no significant discrepancies in the identification of depression between three separate self-report measures completed by patients and semi-structured interviews completed by clinicians. In another study comparing the sensitivity of self-report measures of depression in individuals with dementia, Lichtenberg, Marcopulos, Steiner, & Tabscott (1992) reported that the GDS significantly outperformed clinician-rated measures in accurately identifying depressed patients in the sample when the presence of depression was determined using a psychiatrist's clinical judgement. In a more recent study, it was indicated that patients' self-reported level of depression correlated well with informants' rating of functional impairment, regardless of patients' cognitive functioning (Espiritu et al., 2001).

Considering these discrepant findings, it remains unclear when along the AD continuum patients become anosognostic to their affective symptoms. Additionally, due to certain methodological restrictions, previous studies on self-report measures of depression in AD patients may be limited in terms of the generalizability of their findings. For instance, several studies (Espiritu et al., 2001; Lichtenberg, Marcopulos, Steiner, & Tabscott, 1992; O'Riordan et al., 1990; Ott & Fogel, 1992) relied on a mixed dementia sample, rather than utilizing a pure AD dementia sample. Apart from the etiological makeup of the study sample, some studies were limited in their analysis due to smaller than desired sample sizes or the population from which the sample was derived (Burke et al., 1998; Espiritu et al., 2001; Lichtenberg et al., 1992; Snow et al., 2005). Perhaps even more limiting is the fact that each study assessing depression in AD separated groups of patients into binary levels of impairment (i.e., mildly impaired and severely impaired), rather than classifying them along a larger continuum of impairment that better represents the course of illness in AD (Burke et al., 1998; Espiritu et al., 2001; Müller-Thomsen et al., 2005; Ott & Fogel, 1992; Snow et al., 2005; Verhülsdonk et al., 2013). Moreover, patients in these studies were classified into these two levels of impairment based on their performance on global measures of cognitive functioning, which do not offer adequate information as to their ability to accurately self-report on their depressive symptoms. This in turn limits researchers' ability to identify specific cognitive functions that may mediate their findings.

Study Aims

With the above in mind, this study aims to assess the relationship between self and informant rated symptoms of depression in AD patients in a manner that better captures the progressive cognitive decline in AD. Patients will be placed into one of four levels of cognitive impairment to evaluate precisely where along the AD continuum patient and informant reports diverge from one and other. Groups will be determined based on performance on two global measures of functioning, a composite score derived from performance on tasks of isolated areas of cognition, and performance in isolated domains. In

addition to comparing discrepancy rates when patients are classified by three separate estimates of global cognition, this design will allow us to determine if certain cognitive domains appear more strongly related to the patterns observed than others. Lastly, if a significant discrepancy is found between respondents, this study will explore whether discrepancies between self-reported and informant-reported symptoms vary considerably across levels of impairments.

METHODS

Research Design

This study utilized a multimethod quasi-experimental design to investigate the relationship between patient and informant ratings of depressive symptoms and impairment level in individuals with AD. Participant data were acquired from a case series database maintained by the National Alzheimer's Coordinating Center (NACC). Patients accompanied by informants completed standardized neuropsychological testing and history forms at their respective Alzheimer's Disease Research Centers (ADRC), the results of which were recorded in the NACC initial visit packet for inclusion into the Uniform Data Set (UDS) (Weintraub et al., 2009).

ADRCs are located across the United States and are overseen by their respective institutional review boards (IRB). The NACC functions as a data coordinating center for ADRCs nationwide. Although data collection protocols varied across ADRCs, patients and their co-participants underwent a diagnostic interview at their initial visit, which included obtaining demographic information, medical history, family history, previous neurological exam findings, assessment of functional status, and imaging and genetic testing availability when applicable. Following the results of testing, a determination was made by a clinician or group of clinicians regarding the presence of one or more diagnoses, and their role in contributing to the observed impairments. All of the information collected was recorded in the appropriate data-collection packet, which was returned to the NACC, and entered into their UDS. Additional information regarding data collection protocols for the UDS may found at: https://www.alz.washington.edu/WEB/qaqc_protocol.html.

Participants

Participant case data were procured from the NACC UDS and includes participants from 2005 up until September 2017. Informed consent from participants was obtained at their respective ADRC, and assent and proxy consent were obtained in cases where patients' cognitive impairments precluded them from consenting. Participants were recruited based on the protocol of their local ADRC, which may include referral from clinicians, self-referral, active recruitment, or volunteers. The subsample of the UDS utilized for this study includes healthy controls and patients with cognitive impairment that is primarily due to AD. Due to the nature of the research question(s), patients with incomplete NPI-Qs or GDSs were excluded from the sample. Patients with cognitive impairment due to etiologies other than AD were excluded as well. This was determined using clinicians' best judgement in conjunction with clinical guidelines for diagnosing AD. Additionally, participant data were excluded if patients had a history of post-traumatic stress disorder, bipolar disorder,

schizophrenia spectrum disorder, anxiety disorders, or obsessive-compulsive disorder, as indicated by their history or a clinician's diagnosis.

The initial dataset provided by the NACC included data from 50,131 patient visits (i.e., initial visits and subsequent follow-ups). Among those cases, 17,592 were identified as containing data from an individual's first visit to an ADRC. After filtering out cases that were missing information for patient or informant reports of depressive symptoms and/or performance on global cognitive indicators, the remaining sample comprised data from 16,297 individuals seen at ADRCs spread across the United States.

Measures

The measures used were administered to patients and co-participants in person at the participants' respective ADRCs. Measures were selected from among those first proposed by Weintraub et al. (2009) when designing the UDS neuropsychological testing battery for use at ADRCs across the United States. The battery was initially developed by first reviewing the extant literature to determine the cognitive domains of interest to the NACC's overarching aims, which ultimately included attention, processing speed, executive functioning, episodic memory, and language. Weintraub et al. (2009) then polled participating ADRCs to determine which tests were being used to assess these domains at individual sites. Measures were then selected for inclusion based on frequency of use across sites and final approval from the ADRC Clinical Task Force.

The tests used in this analysis closely resemble the final battery proposed by the Weintraub et al. (2009). Symbol Digit Coding (Wechsler, 1987) was excluded from the analysis due to it being removed from later iterations of the UDS (Weintraub et al., 2018). Vegetable list generation was excluded from analysis due having patients' scores on animal list generation available, which was used by at least 80% of the ADRCs at the time of the UDS's development (Weintraub et al., 2009).

Global Cognitive Functioning—The MMSE (Folstein, Folstein, and McHugh, 1975) was utilized due to it being used in previous studies comparing self and informant-rated depression in individuals with dementia. The MMSE is a psychometrically valid measure for the screening of global cognitive impairment, and Folstein and colleagues (1975) reported the measure had adequate concurrent validity (ranging from 0.66 – 0.77) and test-retest reliability up to 28 days after the first administration (0.98). Other researchers have independently confirmed the tests psychometric properties as well (Tombaugh and McIntyre, 1992).

To ensure consistency in the findings from this study, the CDR® (Morris, 1993) was included in the analyses, which is a measure of global cognition that produces a global score using a scoring algorithm and results of a semi-structured interview with patients and their collateral sources. An online version of the algorithm is available at: https://biostat.wustl.edu/~adrc/cdrpgm/index.html. Hughes, Berg, Danzinger, Coben, and Martin (1982) indicated that the CDR® score correlated well with other global screening instruments (0.74 – 0.84). The global score was shown to have good reliability (0.74) by Burke and colleagues (1988).

Similarly, a composite score of patients' performances on individual tests of memory, auditory attention, working memory, language, processing speed, and executive functioning was calculated to serve as a third measure of global impairment for comparison with the trends observed on the MMSE. This global cognitive composite reflects the average of individuals' Z-scores across measures of isolated cognitive domains.

Attention and Working Memory—Attention and working memory were assessed, respectively, using the forward and backward trials of the Digit Span subtest featured in the Wechsler Memory Scale (WMS-R) and fourth edition of the Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 1987, 2008). Wechsler (2008) reported that the digit span subtest had good convergent validity with other auditory attention and working memory tasks, and relatively high test-retest reliability (0.71 – 0.77). Participants' longest digit sequences correct both forward and backward were utilized in this study.

Processing Speed and Executive Functioning—The Trail Making Test (Reitan & Wolfson, 1993) was used to evaluate information processing speed and executive functioning. Patients' completion times for each trial were included in the analyses. Adequate test-retest reliability was found in part A (0.79), and high test-retest reliability was found in part B (0.89), though these numbers may decrease in neurologically compromised groups (Strauss, Sherman, and Spreen, 2006). The two trails correlate moderately well (0.31) with each other, suggesting the two trials measure related, though separate constructs. The test's link with speed and set-shifting has been demonstrated by its correlation and factor loading with other measures of these constructs (Strauss, Sherman, and Spreen, 2006).

Language Functioning—Two separate tests were used to measure patients' language functioning. The Boston Naming Test (BNT; Goodglass, Kaplan, & Barresi, 2001; Kaplan, Goodglass, and Weintraub, 1983) was included to assess word retrieval for visually presented line drawings of common objects. Patients in this study were administered the 30 odd items from among the original 60 (BNT-30). Williams, Mack, and Henderson (1989) demonstrated that the BNT-30 had good convergent validity with the original 60-item test (0.94 – 0.98), and displayed high internal reliability. Patients' scores on a Semantic (Animal) Fluency task (Lezak, Howieson, Bigler, & Tranel, 2012) was included as well. The task has good face validity, and exploratory factor analysis carried out by Whiteside and colleagues (2016) confirmed the measure's convergent validity. Strauss, Sherman, and Spreen (2006) indicated the test's test-retest reliability in somewhat dependent on the neurological status of an individual at follow-up; however, adequate interrater reliability has been identified in most cases (>0.70).

Learning and Memory—Patients' scores on immediate and delayed recall trials of the Logical Memory subtest from the WMS-R (Wechsler, 1987) were included to indicate learning and memory for verbal information presented in a meaningful context (i.e., episodic memory), respectively. Butters and colleagues (1988) demonstrated the discriminant validity of the Logical Memory subtest in discriminating those with AD from controls. Wechsler (1987) reported the immediate recall trial (0.71) and delayed recall trial (0.75) demonstrated good reliability.

Self-Reported Depressive Symptoms—The GDS is a self-report measure of depression in older-adults initially developed by (Yesavage et al., 1982). It was constructed without an emphasis on the somatic symptoms of depression, and the original scale comprises 30 yes/no items. The 15-item version of the scale (Shiekh & Yesavage, 1986) was utilized in this study, where an endorsement of five or more items suggests the presence of depressive symptomatology. Test-retest reliability of the 15-item GDS after one year is high (>0.84), and internal consistency in healthy adults is adequate (>0.71); however, the internal consistency has been shown to decline with increasing severity of AD (Strauss, Sherman, and Spreen, 2006). The measure has at least moderate convergent validity with other self-report scales of depression (0.59 – 0.90).

Informant Reported Depressive Symptoms—The Neuropsychiatric Inventory-Questionnaire (NPI-Q; Kaufer et al., 2000) is an informant-report questionnaire revised from the Neuropsychiatric Inventory (NPI) (Cummings, 1997). There are 12 yes/no questions that when answered “yes” indicate the presence of neuropsychiatric symptoms, including depression. The measure has been found to have adequate test-retest reliability (0.80), and good convergent validity with its predecessor, the NPI (Kaufer et al., 2000). For this study, the yes/no symptom screener was utilized as an endorsement of depressive symptoms from an informant’s perspective.

Data Treatment

Patients’ raw scores on tests of isolated cognitive domains were converted into Z-scores by subtracting their raw score from the average of the normative sample for the UDS provided by Weintraub et al. (2009), and dividing the resulting value by the standard deviations provided. Four impairment groups (i.e., no impairment, mild impairment, moderate impairment, severe impairment) were then created for each measure, and individuals were sorted into one of the four groups based on scores on global cognitive screening instruments (e.g., MMSE, CDR®), Z-scores on measures of isolated cognitive domains, as well as the global cognitive composite created by the researchers. Cutoffs for placing individuals into impairment groups based on scores on global cognitive screeners were taken from Perneczky et al.’s (2006) study on mapping MMSE scores onto corresponding CDR® scores. Accordingly, MMSE scores of 26 or greater were considered “not impaired,” whereas scores ranging from 25-21, 20-11, and 10 or lower were, respectively, deemed to reflect “mild,” “moderate,” and “severe” levels of impairment. Likewise, CDR® scores ranging from 0.0-0.5 defined the “not impaired” range, and scores of 1.0, 2.0, and 3.0 on this measure indicated “mild,” “moderate,” and “severe” levels of impairment. Impairment group cutoffs for Z-scores on the cognitive composite and domain-specific measures were adapted from Heaton et al.’s classification system (Heaton, Grant, & Matthews, 1991; Heaton, Miller, Taylor, & Grant, 2004). This interpretive method is utilized in the Neuropsychological Assessment Battery (NAB; White & Stern, 2003), and is summarized in table 31.1 of Brooks, Sherman, Iverson, Slick, & Strauss (2011). For domain-specific measures in this study, the “not impaired” range was defined as a Z-score equal to or greater than −1.0. “Mild” impairment was defined as Z-scores ranging from −1.1 - −2.0, “moderate” levels of impairment ranged from −2.1 - −3.0, and “severe” levels of impairment included Z-scores of −3.1 and below.

Scores on the patient-rated GDS were converted into a yes/no categorical variable (i.e., scores of five or more indicate depressive symptoms, whereas scores less than five indicate a denial of these symptoms) to allow for better comparability with informants' yes/no responses to the presence of depressive symptoms on the NPI-Q. A new variable was calculated to examine agreement between patient and informant ratings of depression.

Statistical Analyses

Analyses were performed using a SPSS for Windows (Version 26). Descriptive statistics were run on patients within the participant pool, including: age; gender; ethnicity; level of education; scores on neuropsychological measures; the presence of Alzheimer's disease as indicated by the clinicians; perceived reliability of informants, and the presence of depression as indicated by clinicians, patients, and informants. Using a multimethod approach, a series of Chi-Square tests of independence were performed to determine if there was a significant relationship between patients' level of impairment across each measure, and proportions of agreement and disagreement between patients and informants.

RESULTS

Descriptive statistics for the sample are provided in Table 1. Case data for 8,427 individuals with normal cognition (i.e., healthy controls) and 7,870 individuals with cognitive impairment due to AD were included. The mean age of the 16,297 patients (i.e., healthy controls and individuals with cognitive impairment due to AD) was 72.81 years (*SD* = 10.52) and ranged from 18 to 71. The average number of years of education was 14.94 years (*SD* = 3.46) and ranged from zero to 29 years. The patient sample was made up of 6312 men (38.7%). The racial composition of patients in the sample was 80.6% White, 14.5% Black, 1.9% Asian, 1.0% Latino origin, and 1.0% American Indian. The remaining 1.0% comprises patients whose race was not indicated and those who identified as any of the following: Pacific Islander, Caribbean Islander, Western or Eastern European, Middle Eastern, and Multi-racial. Of informants in the sample, clinicians expressed concerns about the reliability of the information collected from 532 (3.0%) of individuals. 7870 (48.3%) patients in the sample were classified as either being suspected of or having a confirmed AD diagnosis by their respective clinicians. 2429 (14.9%) patients were rated as being actively depressed based on the results of their clinical evaluations. 1950 (12.0%) patients self-identified as being depressed (i.e., GDS scores of five or more), and 4094 (25.1%) of informants rated their respective patients as displaying low mood and/or symptoms of depression.

Average performance on global screening measures and tests of isolated cognitive domains are presented in Table 2 and reported here. The average score on the MMSE was 25.18 (*SD* = 5.62) and ranged from zero to 30. The average global score on the CDR® was 0.50 (*SD* = 0.63) and ranged from 0.0 to 3.0. The average Longest Digit Span Forward length was 6.13 (*SD* = 1.26) and ranged from zero to eight. The average Longest Digit Span Backward length was 4.30 (*SD* = 1.50) and ranged from zero to seven. The average completion time on part A of the Trail Making Test was 50.79 seconds (*SD* = 35.81) and ranged from eight to 150 seconds. The average completion time on part B of the Trail Making Test was 134.09 seconds (*SD* = 89.82) and ranged from 10 to 300 seconds. Average BNT score was 23.59

(*SD* = 6.70) and ranged from zero to 30. The average number of Animals listed in 60 seconds was 15.98 (*SD* = 7.32) and ranged from zero to 77. The average number story units recalled during the immediate recall trial of Logical Memory was 9.31 (*SD* = 5.96), and ranged from zero to 25. The average number of story units recalled after delay was 7.65 (*SD* = 6.30) and ranged from zero to 25.

It warrants mentioning that there were patients within the sample who may reflect outliers relative to the general population (i.e., those with zero years of education, MMSE scores of zero, Animal Fluency scores of 77), and whose results may have disproportionately influenced this study's findings. A sensitivity analysis was therefore performed where these outliers were excluded to determine their impact on the primary and secondary results of this study. The findings from this sensitivity analysis mirrored those obtained when these outliers were included. Given that the primary and secondary analyses appeared unaffected by these outliers, the decision was made to include data from these participants in order to retain the integrity of the sample's representativeness of the population from which it was derived.

Chi-Square analyses were conducted to examine the relationship between global level of impairment in AD and patient-informant agreement regarding the presence of depressive symptoms (See Table 3). When patients were sorted into groups based on MMSE performance, level of impairment appeared significantly associated with changes in patient-informant patterns of agreement (X^2 (6, N = 16297) = 782.23, p = <0.001). Similarly, level of impairment on the clinician rated CDR® was significantly associated with changes in patient-informant agreement across impairment groups (X^2 (6, N = 16297) = 695.72, p = <0.001). The response patterns observed between groups on the CDR® and MMSE were relatively consistent; congruence rates in reporting depressive symptoms showed the greatest decrease between "not impaired" and "mildly impaired" patients, and continued to decline as patient impairment level increased, albeit to a lesser degree. Simultaneously, compared to not impaired patients those in the mildly impaired ranges of the MMSE and CDR® showed more than double the rate of informants indicating depression when patients denied symptoms of the same. Interestingly, greater levels of impairment on both of these measures was also associated with increases in the rate of patients endorsing depressive symptoms when their informants did not do so.

Results of the Chi-Square analyses on patient-informant agreement and impairment level on measures of isolated cognitive abilities as well as an index of overall cognitive functioning are presented in Table 4 and described here. The differences observed in respondent agreement appeared significantly associated with patients' overall composite scores (X^2 (6, N = 13359) = 517.58, p = <0.001). The patterns of patient-informant agreement and disagreement between groups on this index also closely resembled those observed when patients were stratified by level of impairment on both the CDR® and MMSE.

With regard to tests of individual cognitive domains, results indicate that the relationship between level of impairment and patient-informant agreement was statistically significant across measures; however, the strength of this relationship differed between tests. Impairment level on the immediate (X^2 (6, N = 15733) = 805.25, p = <0.001) and delayed (X^2 (4, N = 15697) = 856.94, p = <0.001) recall trials of the Logical Memory subtest were

most strongly associated with changing patterns of respondent agreement across impairment groups. It also bears mentioning that the strength of the relationships observed on each of respective trials of Logical Memory was greater than those observed on both global screening instruments and the composite index of cognitive functioning. Level of impairment on Animal list generation (Animal Fluency) was the third most strongly associated with patterns of patient-informant agreement (X^2 (6, N = 15947) = 488.85, p = <0.001), followed by level of impairment on part B of the Trail Making Test (X^2 (6, N = 13631) = 484.37, p = <0.001). Impairment level on part A of the Trail Making Test (X^2 (6, N = 15365) = 358.74, p = <0.001) and the BNT-30 (X^2 (6, N = 15746) = 316.41, p = <0.001) were the next most strongly associated with the differences observed in respondent agreement across their respective impairment groups. Level of impairment as measured by Longest Digit Span Backward (X^2 (6, N = 15785) = 276.04, p = <0.001) and Longest Digit Span Forward (X^2 (6, N = 15830) = 186.33, p = <0.001) showed the weakest associations with the patterns of patient-informant agreement observed between impairment groups, although were still statistically significant and in the hypothesized direction.

Qualitatively, the patterns of change in patient-informant congruence over the course of impairment were overwhelmingly similar across neuropsychological measures used to quantify patient impairment (see Table 4); rates of patient-informant congruence appeared to decline between those without impairment and mildly impaired patients, and generally continued to decline by relatively smaller increments at subsequent levels of impairment. Additionally, the frequency of informants indicating depressive symptoms when patients denied the same via self-report tended to be greater in worsening levels of impairment. For the majority of the measures used, this difference was most pronounced when comparing not impaired and mildly impaired patients (relative to the frequencies observed between subsequent increases in level of impairment). Similar to patterns observed when patients were classified using global screening measures, rates of patients self-reporting depressive symptoms when informants denied symptoms of the same rose with impairment level.

Overall, patterns of informant-patient congruence over the course of impairment were generally consistent across indices of cognitive functioning. One puzzling trend when considering these results is with respect to the increasing frequency of patients endorsing depressive symptoms when informants denied such. After taking the existing literature into consideration (Brown & Schinka, 2005; Burke et al., 1998; Cacchione et al., 2003; Müller-Thomsen, et al., 2005), informant characteristics were raised as a possible contributor to this finding. Specifically, it was questioned if separating patients by informant-patient relationship types would yield qualitative differences in the response patterns observed between impairment groups. Participants in the dataset were therefore grouped by the informant's relationship to the patient. One group comprised informants who identified as a patient's spouse, partner, companion, or a child, (Partner or Child Informant) and the second included cases where informants identified as siblings, other relatives, friends, neighbors, someone known through family, friends, work, or community, paid caregivers, other, or did not specify their relationship to the patient ("Other" Informant). Descriptive characteristics of these groups were re-evaluated to assess for differences in their clinical presentations. Another set of contingency analyses were then performed on respondent congruence and level of impairment on the MMSE, CDR®, and the immediate and delayed trials of Logical

Memory, as these indices of impairment showed the strongest relationship with agreement and disagreement patterns in the larger sample.

Demographically, patients with partners or children serving as informants had a significantly higher number of men in their group compared with the remainder of patients in the sample (X^2 (1, N = 16297) = 421.72, p = <0.001). This group was also significantly older (t (5247.95) = 7.25, p < 0.001), had AD diagnosed by clinicians in significantly greater frequencies (X^2 (1, N = 16297) = 746.46, p = <0.001), and had significantly higher rates of informants indicating depressive symptoms (X^2 (1, N = 16297) = 69.89, p = <0.001). However, rates of both clinician-rated (X^2 (1, N = 16297) = 2.12, p = 0.124) and patient-rated (X^2 (1, N = 16297) = 0.98, p = 0.322) depression did not differ significantly between groups. Compared to those with partners or children serving as informants, individuals in the "other" informant group had significantly higher rates of clinicians expressing concerns regarding the reliability of information from informants X^2 (1, N = 16297) = 28.78, p = <0.001). Additionally, individuals with partners or children as informants performed significantly worse across global screeners and domain specific measures used in this study, including: the MMSE (t (7210.97) = 22.34, p < 0.001); CDR® (t (7126.32) = 24.92, p < 0.001); Longest Digit Span Forward (t (15828) = 5.25, p < 0.001); Longest Digit Span Backward (t (15783) = 9.08, p < 0.001); Trail Making part A (t (6568.63) = 10.89, p < 0.001) and part B (t (6320.72) = 14.56, p < 0.001); the BNT-30 (t (6712.59) = 12.49, p < 0.001); Animal Fluency (t (6209.92) = 16.67, p < 0.001); and immediate (t (6221.97) = 25.81, p < 0.001) and delayed (t (6086.72) = 25.95, p < 0.001) recall trials of Logical Memory. Descriptive statistics for these groups are presented in Table 5.

The results of the secondary contingency analyses indicated that on global screening measures, the relationship between level of impairment and respondent agreement patterns was significant, regardless of patient-informant relationship type (see Table 6). When impairment level was determined by the MMSE, the observed agreement and disagreement patterns were strongly associated with level of impairment among both patients with partners or children serving as informants (X^2 (6, N = 12621) = 591.62, p = <0.001) and others in the sample (X^2 (6, N = 3676) = 142.60, p = <0.001). Similarly, the association between differing response patterns across CDR® impairment levels was strong among those with informants identifying as patients' partners or children (X^2 (6, N = 12621) = 515.13, p = <0.001) and those with other patient-informant relationship types (X^2 (6, N = 3676) = 137.15, p = <0.001).

Comparable patterns of association were observed when patient performance on the immediate recall trial of Logical Memory was used to classify level of impairment for informant groups; there was a strong relationship between level of impairment and patient-informant agreement patterns among both patients with spouse or child informants (X^2 (6, N = 12142) = 597.64, p = <0.001) and other informant relationship types (X^2 (6, N = 3591) = 169.23, p = <0.001). When level of impairment was determined by performance on the delayed recall trial of Logical Memory, there was again a strong relationship between respondent agreement and impairment level among both those with spouses or children serving as informants (X^2 (4, N = 12109) = 649.99, p = <0.001) and those with other

informant relationship types (X^2 (4, N = 3588) = 164.26, p = <0.001). The relationships observed were all statistically significant. These findings are presented in Table 7.

Although the relationship between impairment level and patterns of patient-informant agreement and disagreement appeared more closely associated among patients with spouses and children serving as informants, it bears mentioning that some of this may owe to differences in group size. It is also worth reiterating that there were significant demographic differences between informant groups which could have affected the relative distributions of patients within the cells of each respective contingency analysis. Despite these differences and the varying strengths of association obtained, the discrepancies between patterns of agreement observed across levels of impairment were largely consistent between informant groups, regardless of the measure used to classify patients' impairment level. The differences between impairment groups were qualitatively similar to those observed in the primary contingency analyses (see Tables 6 and 7); rates of congruent reporting among mildly impaired patients were lower than those observed in not impaired patient, and generally continued to decline over the course of impairment. Concurrently, compared to those who were not impaired, instances of informants rating patients as depressed when patients denied the same were more frequent across levels of impairment. Lastly, despite splitting the sample by informant-type, rates of patients endorsing depression when their informants denied the same again generally tended to increase with each subsequent impairment level.

DISCUSSION

This study examined how varying degrees of impairment as indicated by three separate indicators of global functioning (e.g., MMSE, CDR®, Cognitive Composite Index) influenced patterns of patient-informant congruence in reporting depressive symptoms. To date, research regarding the relationship between cognitive impairment and affective anosognosia in individuals with AD has provided varying results. Some have proposed that the accuracy of patients' ratings of depressive symptoms is unattenuated by level of cognitive impairment (Burke et al., 1992; Carvalho et al., 2013; Feher et al., 1992; Lichtenberg et al., 1992; O'Riordan et al., 1990); however, there is mounting evidence to suggest that worsening impairment and reductions in insight in AD significantly impacts agreement between patient self-reported symptoms and observer reports (Burke et al., 1998; Frank et al., 2011; Müller-Thomsen et al., 2005; Ott & Fogel, 1992; Verhülsdonk et al., 2013). That said, it is unclear at what stage of AD patients begin to significantly underreport depressive symptoms. This may be in part due to studies on anosognosia in AD relying on a binary system to classify individuals into impairment groups (Chung & Man, 2009; (Chung & Man, 2009; Galeone, Pappalardo, Chieffi, Iavarone, & Carlomagno, 2011; Oba et al., 2018).

Across global indicators used in this study, level of impairment was significantly associated with patient-informant congruence, and the patterns observed did not appear to differ substantially based on the method used to quantify global impairment. Qualitatively, as level of impairment worsened, patient-informant agreement regarding the presence of depressive symptoms decreased. Simultaneously, rates of informants who reported observing depressive

symptoms when patients denied the same increased alongside worsening levels of impairment. When progressing along the impairment continuum for each global indicator, intergroup discrepancies in the rates of these respective phenomena were largest between not impaired and mildly impaired patients. These results indicate that even at the mildest stages of global impairment in AD (i.e., MMSE ≤ 25, CDR® ≥ 1), patient and informant agreement regarding depressive symptoms substantially decreases and continues to subtlety decline as impairment increases. With regard to clinical implications, these findings suggest that informant-reports are invaluable resources to supplement information collected from patients with AD, even at the earliest stages of impairment.

Apart from examining the relationship between respondent agreement and level of impairment as measured by global indicators, another primary goal of this study was to evaluate the relationship between patient-informant agreement and level of impairment within isolated cognitive domains (e.g., attention, working memory, processing speed, executive functioning, language, episodic memory). Specifically, this study sought to examine if patterns of patient-informant congruence over the course of impairment differed between cognitive domains, and if the patterns observed were more strongly associated with performance within certain cognitive domains relative to others. Overall, response patterns over respective gradients of impairment were remarkably similar across cognitive domains, and were largely consistent with the trends observed when using global indicators to classify impairment (i.e., performances more than one standard deviation below the mean were associated with reductions in respondent agreement). Level of impairment in each of the domains appeared significantly associated with changes observed in patient-informant agreement as well; however, certain cognitive domains demonstrated a stronger relationship with their respective patterns than others. In particular, episodic memory overwhelmingly showed the strongest association with changes in informant-patient agreement; on the other hand, auditory attention and working memory appeared least associated with the respective response patterns observed. Apart from lending further support to the notion that even mild levels of impairment significantly alter rates of patient-informant agreement, findings from the domain-specific analyses suggest that episodic memory, which is commonly among the first cognitive abilities impacted in AD (DeFina et al., 2013; Weintraub et al., 2012; Zillmer et al., 2007), plays a critical mediating role in patient-informant agreement/disagreement regarding the presence of depressive symptoms. As such, when even subtle declines in this ability are suspected, it is incumbent upon clinicians to corroborate patients' reporting by obtaining information from informants.

While addressing the primary research questions, an unexpected finding emerged which remains unexplained; as level of impairment increased, rates of patients reporting depressive symptoms when informants denied observing features of the same increased as well. Although patient-informant pairs who fit within this trend reflect a relatively small percentage of their respective impairment groups, it is certainly remarkable that across global and domain specific measures, their relative proportion tended to increase as impairment worsened. Based on previous research (Burke et al., 1998; Cacchione et al., 2003; Frank et al., 2011; Müller-Thomsen et al., 2005), it was suspected that separating individuals by patient-informant relationship type would help account for this finding. However, patterns of patient-informant agreement and disagreement when informants

identified as spouses/partners or children were similar to those observed when informants consisted of siblings, other relatives, friends, neighbors, paid caregivers, people known through family, friends, work, or community, and those who did not specify their relationship to the patient. This may be advantageous clinically, as it suggests that a variety of informants may offer insights similar to those of close family members; however, this study was nonetheless unable to explain the rising rates of patients reporting depressive symptoms when informants denied observing the same. One possibility may be patients in this category incorrectly endorsed depressive symptoms on the GDS (i.e., false positives), and the rise in this trend reflects increased instances of false positive reporting as a function of variable item endorsement as impairment level worsens. Alternatively, it is possible that some of these patients reflect individuals who may have previously experienced prolonged periods of depression which have become less severe in the context of positivity effects seen in older adults and those with dementia (Bohn, Kwong See, & Fung, 2016; Gorenc-Mahmutaj et al., 2015), leading informants to perceive them as being less depressed relative to their baseline.

Overall, the results of this study support the presence of a significant relationship between patterns of patient-informant agreement and level of impairment on both global and domain-specific measures. Findings also indicate that mild levels of impairment are associated with the largest reductions in patient-informant agreement. While all cognitive domains demonstrated some relationship with changes in respondent agreement, the results of this study suggest that episodic memory is the most closely associated in this regard. Patterns of agreement and disagreement did not appear to differ based on patient-informant relationship type.

Strengths and Limitations

The design of this study has several strengths that lend further legitimacy to its findings. Firstly, this study utilized a multimethod method approach consisting of multiple global and domain-specific performance-based measures, as well as an interview-based global screener. In doing so, this study can more definitively state that the results validly reflect the relationship of interest. Similarly, the size of the sample in the primary analyses was such that it enhanced the ability to detect any statistically significant findings that may have been present. The group-sizes for those with more severe levels of cognitive impairment were admittedly rather small in some cases; however, the consistent patterns observed in the relatively larger groups suggest this may not have drastically altered results of the primary analyses. This is particularly important, as small sample sizes were raised as a limitation of numerous other studies of anosognosia (Burke et al., 1998; Espiritu et al., 2001; Lichtenberg, et al., 1992; O'Riordan et al., 1990; Ott & Fogel, 1992; Snow et al., 2005). Likewise, many previous studies have been limited by their use of mixed dementia samples, thereby reducing the generalizability of their findings to the larger AD population. Contrastingly, this study utilized strict exclusion and inclusion criteria to ensure the findings may be broadly applicable to individuals with AD. This also reduced potential statistical noise that may have interfered with the results.

Despite the methodological advantages of this study, there are still a number of limitations that merit discussion. Due to this study's reliance on an existing dataset, the researchers were unable to collect certain variables or design the ways in which those available were collected. As such, while this study included patient and informant perspectives regarding the presence of depression, it did not include a variable to reflect clinicians' perspectives due to uncertainty that their determinations were made independent of patient and informant responses. This marks a shortcoming of the present study, as unlike others (Müller-Thomsen et al., 2005; Ott & Fogel, 1992; Snow et al., 2005; Verhülsdonk et al., 2013), the researchers could not compare patients' and informants' responses to a "gold standard" to evaluate the accuracy of their reporting. Further, this study has made inferences regarding possible losses of insight into affective symptoms on the basis of patient-informant disagreement; however, due to lacking an objective measure of insight, this study is limited in its ability to definitively say that these discrepancies reflect increases in the rates of anosognosia, versus other potential mediators, including: heterogeneity in subjective perception of depressive symptoms; quality of patients' disclosures of depressive symptoms as impairment level increases; patients' baseline levels of depression prior to experiencing declines due to AD; and differences between the GDS and NPI-Q in terms of item count and content.

Other limitations stem from the significant differences between groups when the sample was separated by relationship type for the secondary analyses. Notably, there were more than three times as many patients with partners or children serving as informants than others in the sample, which potentially skewed the relative cell sizes in subsequent contingency analyses. There were also significant demographic differences between the two groups, including: relative gender distributions; age; rates of AD diagnoses; and rates of informants indicating the presence of depression. Additionally, those with partners or children as informants performed significantly worse across all measures. All that being said, response patterns over the course of impairment appeared qualitatively similar between the groups, suggesting patient-informant relationship type had no effect on the primary findings. And while this study would certainly not be the first failing to establish a link between informant characteristics and patient-informant response discrepancies (Snow et al., 2005; Verhülsdonk et al., 2013), findings from other studies have argued the contrary (Cacchione et al., 2003; Müller-Thomsen et al., 2005). Therefore, the possibility that the disparate group sizes and/or significant demographic and cognitive differences between respondent groups may have affected the patterns observed in the secondary analyses cannot be dismissed.

Future Directions

Future studies on the relationship between cognitive functioning and patient-informant response patterns should continue to stage participants along a larger continuum of impairment, similar to what was attempted here. Likewise, future studies should consider a multimethod approach (i.e., inclusion of global and domain-specific measures), as it offers a more nuanced understanding of how various cognitive domains are related to changes in respondent agreement. In relation to this idea, given that insight has been reported as a significant mediator of discrepancy patterns (Ott & Fogel, 1992; Snow et al., 2005), studies seeking to replicate these findings should consider including a formal insight / deficit awareness scale into their analysis. Additionally, future studies should aim to address some

of the major shortcomings of the present study. Specifically, forming more homogeneous groups when evaluating respondent agreement by informant-relationship type, and including objective clinical ratings of the presence of depression.

Apart from these suggestions, future studies should also investigate instances of patients reporting depression when informants denied observing significant depressive behaviors. As has been commented on previously, patient-informant dynamics may play a role in rates of agreement and disagreement. We attempted to evaluate this using the informant-patient relationship type as one potential indicator of these dynamics; however, this study was ultimately unable to explain the steadily rising rates of this phenomena as impairment worsened. It will be important to see if future researchers replicate this finding, or if the current results reflect an anomaly within the sample. If others independently corroborate this unexpected finding, it may warrant more rigorous investigation into the possible contributors, such as the length of the patient-informant relationship, or even the informant's emotional state at the time of the evaluation. Future studies should therefore collect this information and include it in their analyses to determine if these factors play a role in patterns of agreement and disagreement.

Lastly, one of the major advantages of this study was the utilization of a large sample of individuals with cognitive impairment due to AD, versus using a sample comprised of various etiologies of impairment. In doing so, these results likely better reflect the relationship between cognitive impairment in AD and patient-informant response patterns. However, this also comes at the cost of being able to infer how the relationship between patient-informant agreement might differ in cases of other neurodegenerative disorders. Future research should therefore aim to replicate this study using samples of patients with other sources of acquired progressive cognitive impairment (e.g., cerebrovascular factors, Parkinson's disease, traumatic brain injury, dementia with Lewy Bodies, autoimmune disorders, substance-use related, etcetera), particularly those with less direct involvement of the episodic memory system.

CONCLUSIONS

This study investigated the relationship between patient and informant ratings of depression and cognitive impairment in AD. In addition to finding a significant relationship between the two, this study's unique staging of impairment across a spectrum allowed for direct comparison of patient-informant response patterns at various levels of impairment in AD. As a result, the findings show how worsening cognitive impairment is associated with decreases in patient-informant congruence and increases in rates of patients denying depression when informants endorsed observing features of the same. Moreover, this study identified that changes in these trends are most pronounced at the mildest stages of cognitive impairment, which contrasts findings from other studies suggesting that patients in the mild and moderate stages of AD accurately self-report depressive symptoms. By using a collection of domain-specific measures, this study identified that episodic memory is most closely associated with changes in respondent agreement over the course of impairment, suggesting this ability plays a large role in mediating patient insight into their symptoms. The researchers hope that clinicians will learn of these findings and take steps to collect corroborating information

from informants when even subtle declines are suspected in AD patients. Results from the secondary analyses suggest a variety of individuals may serve as informants and offer valuable observations regarding potentially meaningful changes in patient mood and behavior. Therefore, in cases when immediate family members are unavailable, or relying on them as informants seems inappropriate, clinicians (and patients) may benefit from considering alternative sources of corroborating information.

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KEY POINTS

Question:

At what point along the Alzheimer's disease (AD) continuum do patients significantly differ from informants in their reporting of depressive symptoms, and what, if any, cognitive abilities may mediate this relationship?

Findings:

Worsening cognitive impairment was significantly associated with decreases in patient-informant agreement, and episodic learning and memory functioning were most closely associated with discrepancies in respondent agreement.

Importance:

Even at the earliest stages of AD, clinicians should take steps to obtain corroborating information regarding the presence of depressive symptoms from caregivers (e.g., family members, friends, neighbor, co-workers, paid caregiver, etc.).

Next Steps:

Future studies on the relationship between cognitive functioning and patient-informant response patterns should continue to stage participants along a larger continuum of impairment and incorporate a multimethod approach, as this allows for a far more nuanced understanding of findings.

Table 1

Descriptive Statistics

Characteristic	N(%)	M	SD	Range
Patient's Age on Day of Testing	—	72.81	10.52	18-104
Years of Education	—	14.94	3.46	0-29
Gender, Male	6312 (38.7)	—	—	—
Race				
White	13141 (80.6)	—	—	—
Black	2361 (14.5)	—	—	—
Asian	306 (1.9)	—	—	—
Latino	165 (1.0)	—	—	—
American Indian	145 (1.0)	—	—	—
Other[†]	179 (1.0)	—	—	—
Concerns Regarding Informant Reliability, Clinician Judgement	532 (3.0)	—	—	—
AD Suspected or Confirmed, Clinician Diagnosis	7870 (48.3)	—	—	—
Active Depression, Clinician Diagnosis	2429 (14.9)	—	—	—
GDS ≥ 5	1950 (12.0)	—	—	—
NPI-Q, Depression Indicated	4094 (25.1)	—	—	—

[†]"Other" reflects groups with n's < 100 (e.g., Pacific Islander, Caribbean Islander, Western or Eastern European, Middle Eastern, Multi-racial, Unspecified)

Table 2

Total Sample Neuropsychology Battery Scores

Cognitive Measure	N†	M	SD	Range
MMSE	16297	25.18	5.62	0-30
CDR Global Score	16297	0.50	0.63	0-3
Longest Digit Span Forward	15830	6.31	1.26	0-8
Longest Digit Span Backward	15785	4.3	1.50	0-7
Trails A (seconds)	15365	50.79	35.81	8-150
Trails B (seconds)	13631	134.09	89.82	10-300
BNT-30	15746	23.59	6.70	0-30
Animal Fluency	15947	15.98	7.32	0-77
Logical Memory Immediate	15733	9.31	5.96	0-25
Logical Memory Delayed	15697	7.65	6.30	0-25

†Some patients were unable to complete all measures in the neuropsychological battery due to physical and/or cognitive impairments.

Table 3

Relationship Between Performance on Global Measures and Patient-Informant Congruence in Reporting Depression

Agreement/ Disagreement type	Not Impaired (MMSE≥26)		Mild (MMSE=25-21)		Moderate (MMSE=20-11)		Severe (MMSE≤10)			
	n	%	*n*	%	*n*	%	*n*	%	χ^2	*df*
Congruent Reporting	8463	83.8	2136	68.1	1675	63.6	259	60.2		
Informant Yes x Self No	1209	12.0	834	26.6	782	29.7	129	30.0	782.23*	6
Informant No x Self Yes	425	4.2	165	5.3	178	6.8	42	9.8		
	Not Impaired (CDR =0-0.5)		**Mild (CDR=1)**		**Moderate (CDR=2)**		**Severe (CDR=3)**			
	n	%	*n*	%	*n*	%	*n*	%	χ^2	*df*
Congruent Reporting	9495	82.3	2221	63.8	713	64.4	104	59.1		
Informant Yes x Self No	1535	13.3	1050	30.2	315	28.4	54	30.7	695.72*	6
Informant No x Self Yes	502	4.4	210	6.0	80	7.2	18	10.2		

* $p < 0.001$

Table 4

Relationship Between Performance on Isolated Measures of Cognition and Patient-Informant Congruence in Reporting Depression

Agreement/Disagreement type	Not Impaired (Z ≥ −1.0)		Mild (Z = −1.1 - −2)		Moderate (Z = −2.1 - −3.0)		Severe (Z ≤ −3.1)			
	n	%	*n*	%	*n*	%	*n*	%	χ^2	*df*
Cognitive Composite Score										
Congruent Reporting	7546	84.9	1838	70.6	952	66.4	276	63.9		
Informant Yes x Self No	1015	11.4	629	24.2	393	27.4	119	27.5	517.58*	6
Informant No x Self Yes	330	3.7	135	5.2	89	6.2	37	8.6		
Longest Digit Span Forward										
Congruent Reporting	9581	79.5	1798	71.7	692	65.9	130	61.0		
Informant Yes x Self No	1958	16.2	554	22.1	277	26.4	63	29.6	186.33*	6
Informant No x Self Yes	520	4.3	156	6.2	81	7.7	20	9.4		
Longest Digit Span Backward										
Congruent Reporting	9258	80.4	2031	70.2	694	63.1	196	71.3		
Informant Yes x Self No	1772	15.4	681	23.5	317	28.8	61	22.2	276.04*	6
Informant No x Self Yes	487	4.2	182	6.3	88	8.0	18	6.5		
Trails A										
Congruent Reporting	8587	81.5	1221	73.3	579	70.4	1527	65.1		
Informant Yes x Self No	1531	14.5	339	20.3	209	25.4	646	27.5	358.74*	6
Informant No x Self Yes	413	3.9	106	6.4	34	4.2	173	7.4		
Trails B										
Congruent Reporting	7722	84.4	862	73.3	462	72.8	1765	66.1		
Informant Yes x Self No	1100	12.0	235	20.0	142	22.4	732	27.4	484.37*	6
Informant No x Self Yes	326	3.6	79	6.7	31	4.8	175	6.5		
BNT-30										
Congruent Reporting	8323	81.4	1177	73.2	772	68.1	1882	67.7		
Informant Yes x Self No	1490	14.6	337	20.9	294	25.9	705	25.4	316.41*	6
Informant No x Self Yes	410	4.0	95	5.9	68	6.0	193	6.9		
Animal Fluency										
Congruent Reporting	7479	83.2	3039	71.3	1455	66.0	314	63.4		
Informant Yes x Self No	1164	13.0	982	23.0	593	26.9	132	26.7	488.85*	6
Informant No x Self Yes	341	3.8	242	5.7	157	7.1	49	9.9		
Logical Memory Immediate										
Congruent Reporting	6158	86.0	2167	78.2	2034	68.2	1775	63.1		
Informant Yes x Self No	734	10.2	462	16.7	770	25.8	861	30.6	805.25*	6
Informant No x Self Yes	272	3.8	143	5.1	179	6.0	178	6.3		
Logical Memory Delayed										
Congruent Reporting	6350	86.3	2028	77.8	3741	65.3	—	—		
Informant Yes x Self No	738	10.0	427	16.4	1642	28.7	—	—	856.94*	4

Agreement/Disagreement type	Not Impaired (Z ≥ −1.0)		Mild (Z = −1.1 - −2)		Moderate (Z = −2.1 - −3.0)		Severe (Z ≤ −3.1)			
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	χ^2	*df*
Informant No x Self Yes	270	3.7	153	5.8	348	6.0	—	—		

* $p < 0.001$

Table 5

Descriptive Statistics When Participants Are Separated by Patient-Informant Relationship

Characteristic	Partner or Child Informant (*n* = 12,621)			"Other" Informant (*n* = 3676)					
	N (%)	*M*	*SD*	*N (%)*	*M*	*SD*	χ^2	*t*	*P*
Gender, Male	5422 (43.0)	—	—	890 (24.2)	—	—	421.72	—	<0.001
AD Suspected or Confirmed, Clinician Diagnosis	6832 (54.1)	—	—	1038 (28.3)	—	—	764.46	—	<0.001
Active Depression, Clinician Diagnosis	1909 (15.1)	—	—	520 (14.2)	—	—	2.12	—	0.124
Concerns Regarding Informant Reliability, Clinician Judgement	373 (3.0)	—	—	159(4.3)	—	—	28.78	—	<0.001
NPI-Q, Depression Indicated	3364 (26.7)	—	—	730(19.9)	—	—	69.89	—	<0.001
GDS ≥ 5	1493 (11.8)	—	—	457(12.4)	—	—	0.98	—	0.322
GDS Total Score	—	1.89	2.36	—	1.83	2.46	—	1.40	0.161
Age on day of testing	—	73.17	10.02	—	71.59	12.02	—	7.25	<0.001
Years of Education	—	14.92	3.45	—	15.01	3.52	—	1.33	0.183
Neuropsychology Battery									
MMSE	—	24.72	5.77	—	26.79	4.70	—	22.34	<0.001
CDR Global Score	—	0.55	0.64	—	0.295	0.53	—	24.92	<0.001
Longest Digit Span Forward	—	6.29	1.27	—	6.41	1.23	—	5.25	<0.001
Longest Digit Span Backward	—	4.25	1.45	—	4.49	1.42	—	9.08	<0.001
Trails A (seconds)	—	52.37	36.78	—	45.48	31.75	—	10.89	<0.001
Trails B (seconds)	—	139.84	92.29	—	115.82	78.74	—	14.56	<0.001
BNT-30	—	23.26	6.88	—	24.71	5.90	—	12.49	<0.001
Animal Fluency	—	15.47	7.35	—	17.69	6.95	—	16.67	<0.001
Logical Memory Immediate	—	8.68	5.93	—	11.44	5.55	—	25.81	<0.001
Logical Memory Delayed	—	6.97	6.24	—	9.95	5.98	—	25.95	<0.001

Table 6

Relationship Between Performance on Global Measures and Patient-Informant Congruence in Reporting Depression When Grouped by Patient-Informant Relationship

Agreement/Disagreement type	Not Impaired (MMSE≥26)		Mild (MMSE=25-21)		Moderate (MMSE=20-11)		Severe (MMSE≤10)			
	n	%	*n*	%	*n*	%	*n*	%	χ^2	*df*
Spouse/Children										
Congruent Reporting	6052	83.4	1828	67.6	1451	63.5	227	59.6		
Informant Yes x Self No	927	12.8	735	27.2	687	30.1	118	31.0	591.62*	6
Informant No x Self Yes	273	3.8	140	5.2	147	6.4	36	9.4		
"Other"										
Congruent Reporting	2411	84.8	308	71.3	224	64.0	32	65.3		
Informant Yes x Self No	282	9.9	99	22.9	95	27.1	11	22.5	142.60*	6
Informant No x Self Yes	152	5.3	25	5.8	31	8.9	6	12.2		
	Not Impaired (CDR =0-0.5)		**Mild (CDR=1)**		**Moderate (CDR=2)**		**Severe (CDR=3)**			
	n	%	*n*	%	*n*	%	*n*	%	χ^2	*df*
Spouse/Children										
Congruent Reporting	6897	81.7	1951	63.7	617	64.1	93	60.0		
Informant Yes x Self No	1204	14.3	934	30.5	281	29.2	48	31.0	515.13*	6
Informant No x Self Yes	340	4.0	178	5.8	64	6.7	14	9.0		
"Other"										
Congruent Reporting	2598	84.1	270	64.6	96	65.7	11	52.4		
Informant Yes x Self No	331	10.7	116	27.8	34	23.3	6	28.6	137.15*	6
Informant No x Self Yes	162	5.2	32	7.6	16	11.0	4	19.0		

* $p < 0.001$

Table 7

Relationship Between Performance on Logical Memory and Patient-Informant Congruence in Reporting Depression When Grouped by Patient-Informant Relationship

Agreement/Disagreement type	**Not Impaired (Z ≥ −1.0)**		**Mild (Z = −1.1 - −2)**		**Moderate (Z = −2.1 - −3.0)**		**Severe (Z ≤ −3.1)**			
	n	***%***	***n***	***%***	***n***	***%***	***n***	***%***	χ^2	***df***
Spouse/Children										
Congruent Reporting	4280	86.0	1622	77.0	1746	67.8	1576	63.4		
Informant Yes x Self No	528	10.6	386	18.3	680	26.4	760	30.6	597.64*	6
Informant No x Self Yes	170	3.4	98	4.7	148	5.8	148	6.0		
"Other"										
Congruent Reporting	1878	85.9	545	81.8	288	70.4	199	60.3		
Informant Yes x Self No	206	9.4	76	11.4	90	22.0	101	30.6	169.23*	6
Informant No x Self Yes	102	4.7	45	6.8	31	7.6	30	9.1		
Logical Memory Delayed	**Not Impaired (Z ≥ −1.0)**		**Mild (Z = −1.1 - −2)**		**Moderate (Z = −2.1 - −3.0)**		**Severe (Z ≤ −3.1)**			
	n	***%***	***n***	***%***	***n***	***%***	***n***	***%***	χ^2	***df***
Spouse/Children										
Congruent Reporting	4406	86.5	1534	76.3	3267	65.3	—	—		
Informant Yes x Self No	522	10.3	363	18.1	1451	29.0	—	—	649.99*	4
Informant No x Self Yes	165	3.2	114	5.7	287	5.7	—	—		
"Other"										
Congruent Reporting	1944	85.9	494	82.8	474	65.3	—	—		
Informant Yes x Self No	216	9.5	64	10.7	191	26.3	—	—	164.26*	4
Informant No x Self Yes	105	4.6	39	6.5	61	8.4	—	—		

*$p < 0.001$