FACTOR STRUCTURE OF THE GERIATRIC DPERESSION SCALE AND ITS RELATIONSHIP TO COGNITION IN ALZHEIMER'S DISEASE

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A Thesis

Presented to

The Faculty of the Department

of Psychology

University of Houston

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In Partial Fulfillment

Of the Requirements for the Degree of

Master of Arts

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By

Whitney Havins

December, 2011

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ABSTRACT

Evidence suggests that patients with Alzheimer's disease (AD) experience more frequent and severe apathy and depression than their healthy age counterparts. Moreover, some studies have shown that apathy and depression are associated with greater cognitive and functional decline in these patients. Previous research has shown the Geriatric Depression Scale to be capable of identifying symptoms of both apathy and dysphoria in older adults. However, no study to date has systematically explored whether the Geriatric Depression Scale measures symptoms of apathy and dysphoria in patients with AD and related these constructs to performance on neuropsychological measures. This study employed exploratory factor analysis to identify factors of the Geriatric Depression Scale in a sample of 569 patients with pure probable AD. A four-factor solution was obtained, yielding factors associated with apathy, dysphoria, social withdrawal, and cognitive impairment. It was hypothesized that symptoms of apathy would be associated with cognitive and functional impairment, even after controlling for dysphoria. Two-way ANOVAs showed that endorsement of Apathy factor items was associated with greater impairment in verbal memory and motor speed, as well as functional impairment. Dysphoria was not associated with any cognitive or functional variables. Findings suggest that the GDS may be used as a screening measure for symptoms of apathy in AD, hopefully aiding early identification and intervention to reduce patient and caregiver burden.

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Introduction

Depression in Alzheimer's Disease: Definition and Prevalence

Alzheimer's disease (AD) is a progressive dementia characterized by impaired memory, impairment in at least one other cognitive domain, and loss of functional abilities. The hallmark cognitive changes in AD are often accompanied by noncognitive or psychiatric disturbances that include depression, apathy, hallucinations, delusions, irritability, anxiety, and sleep disturbances. According to Lyketsos and Olin (2002), the prevalence of these disturbances among patients with AD has been estimated to be three to four times higher than that seen in comparably aged persons without dementia.

The high incidence of depression, in particular, has made it the subject of much research over the past two decades. Most clinical studies report the prevalence of depression to be 30-50% in individuals with AD, with prevalence estimates ranging from 1-86% (Zubenko et al., 2003). The variance in these estimates from clinical studies can likely be explained by differences in operational definitions, methodology, diagnostic criteria, and assessment of depression. According to Payne et al. (1998), depressive features are present in 30-50% of patients with probable AD, whereas Major Depressive Disorder (MDD) diagnosis applies to 22% and minor depression or dysthymia diagnoses apply to 27% of persons with probable AD. Population studies also confirm a high incidence of depression in patients with AD (Lee & Lyketsos, 2003). As noted above, depression rates in older adults (> 65 years of age) with AD are significantly higher than in their healthy counterparts (Ross, Arnsberger, & Fox, 1998).

The Complex Nature of Diagnosing Depression in AD

Depression in the elderly is particularly difficult to diagnose, as it must be distinguished from somatic illness and normal correlates of the aging process (Adams, 2001). Symptoms of depression must be distinguished from those of dementia and apathy. In particular, the vegetative symptoms of depression may also characterize dementia (Landes, Sperry, & Strauss, 2005), and loss of interest is a symptom of both apathy and depression. Thus, in patients with AD, investigators and clinicians are faced with the task of disentangling the presence and contributions of dementia, depression, and apathy to cognitive and functional impairment. Moreover, this symptom overlap may be responsible for under-recognition or spurious inflation of depression prevalence estimates in AD.

Research suggests that symptomatology may distinguish depression in AD from depression in non-demented elderly persons. Zubenko et al. (2003) found that AD patients and non-demented elderly subjects experienced similar numbers of depressive features during their most recent major depressive episode. However, patients with AD were significantly more likely to report diminished ability to concentrate or indecisiveness and significantly less likely to have experienced sleep disturbance or feelings of worthlessness or guilt. In addition, 30.9% of AD patients experienced delusions or hallucinations during the course of their major depressive episode, whereas none of the non-demented elderly subjects experienced psychotic symptoms.

In addition to the difficulties inherent in distinguishing depression in AD from other behavioral syndromes and dementia itself, uncertainties exist regarding the course, etiology, and diagnostic criteria for depression in AD. Evidence suggests that the presence and severity of depressive symptoms may change during the course of AD. Although several studies have

attempted to predict these changes, no consensus has been reached regarding the onset, progression, and persistence of depression in AD. Müller-Thomsen, Arlt, Mann, Maβ, and Ganzer (2005) found that the prevalence of depression was consistently higher in patients with moderate to severe AD than it was in patients with mild AD across four different scales of depression. The results of the study lend support to the idea that the presence of depressive symptoms may be positively related to the severity of the disease and cognitive impairment. Conversely, Zubenko et al. (2003) found that the largest increase in the proportion of subjects who experienced a major depressive episode (MDE) occurred in patients with the mildest cognitive impairment, suggesting that depression may develop most frequently in the earliest stages of AD and become less frequent with increasing severity. Moreover, when comparing symptom prevalence across disease severity, Zubenko et al (2003) found no significant increase in number of symptoms or changes in the pattern of symptom endorsement. Other studies have failed to find any relationship at all between severity of depression and level of cognitive impairment (Lee & Lyketsos, 2003). This potential variance in depression severity across disease severity complicates assessment and requires further investigation.

Moreover, issues abound in the accuracy of patient and caregiver reports regarding depression in AD. First, patients who suffer from a dementing illness may not be able to accurately reflect their emotional state, particularly in the most severe stages of the disease. Although caregiver reports pose a potential solution to this problem, it is important to note that caregivers tend to rate AD patients as more depressed than do patients themselves. Research suggests that caregivers of AD patients have higher rates of depression and may be endorsing symptoms that better reflect their own mood (Chemerinski, Petracca, Sabe, Kremer, & Starkstein, 2001).

In addition to the complexities outlined above, diagnosis is complicated by the unclear (and potentially multifactorial) etiology of depression in AD. Some authors have suggested that depression within the context of AD may be reactive depression. In other words, patients who receive an AD diagnosis or who become aware of their own cognitive and functional decline may experience symptoms of depression. This hypothesis is built upon the assumption that patients with AD possess insight into their cognitive difficulties and prognosis. On the contrary, Derouesne et al. (1999) found that only 25% of patients with mild AD were aware of their cognitive deterioration. Moreover, studies show that insight is not a predictor of depression in AD. Lee and Lyketsos (2003) suggest that dysthymia is more frequently associated with insight into cognitive decline, whereas Major Depressive Disorder is more likely to be associated with biological factors.

Depression in AD may simply be a recurrence of previous major depressive episodes (MDEs) experienced in early or midlife. Given that at least 60% of individuals who experience a single MDE can be expected to have a second episode and that number of prior MDEs predicts subsequent MDEs (American Psychiatric Association, 2000), it is possible that depression in AD may occur independently of AD itself. Regardless of whether or not depression is a risk factor for the development of dementia, there is no reason that MDEs experienced before the onset of cognitive decline should cease to recur within the course of AD (Lee & Lyketsos, 2003).

There is also evidence to suggest a pathophysiology shared by depression and AD. This hypothesis of a shared etiology is supported by the close temporal relationship between late-onset depression and dementia and the likelihood of patients who experience late-onset depression to develop dementia (Lee & Lyketsos, 2003). Investigators have identified

particular areas of neuronal loss associated with AD that may also be responsible for the incidence of depression in AD. Zubenko et al. (2003) found that depression in AD is directly related to the disproportionate degeneration of the brainstem aminergic nuclei (in particular, the locus coeruleus and dorsal raphe nucleus) that occurs within the course of AD. They also cited evidence for relative preservation of the nucleus basalis of Meynert and its cholinergic projections in patients with comorbid depression and AD. Of note, Zubenko (2000) asserted that this finding may contribute to a relative decrease in depression prevalence with loss of cholinergic function over the course of AD. Ultimately, Zubenko et al. (2003) concluded that this particular pattern of neuropathology and the neurochemical disruption that results are specific to depression in AD and are not related to other behavioral or perceptual disturbances or to overall neurodegeneration, as measured by duration of illness, brain weight, and densities of senile plaques and neurofibrillary tangles.

Other authors have proposed a connection between vascular disease, AD, and depression. According to Alexopoulos et al. (1997), depression may be associated with subcortical lesions that disrupt frontostriatal circuits and their connections to the limbic system and hippocampus. Although the prevalence of vascular depression in AD is not yet known, researchers have identified similar risk factors for both. White matter hyperintensities and evidence of the subcortical lesions described above have been found in AD, vascular dementia, and geriatric depression. Although vascular changes and cognitive impairment might be generally associated with vascular dementia, Wright and Persad (2007) suggest that the boundary between vascular dementia and AD may not be as distinct as originally imagined. Vascular risk factors have been related to AD and may actually potentiate neuropathological changes traditionally associated with AD (Breteler, 2000). This shared

underlying neurobiology may be most appropriately applied to a frontal variant of AD, characterized by early impairment in executive function and psychomotor speed and more severe behavioral disturbance.

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction and hypercortisolemia may also represent a link between depression and AD. HPA axis dysregulation has been associated with cognitive impairment and mood disorders. Elevated glucocorticoid levels have also been associated with neuronal atrophy, particularly in the hippocampus and prefrontal cortex, areas of the brain commonly associated with depression and AD (Sotiropoulos, Cerqueira, Catania, Takashima, Sousa, & Almeida, 2008). Interestingly, higher basal cortisol levels have been reported in patients with AD than in their healthy elderly counterparts (Csernansky et al., 2006; Souza-Talarico, Chaves, Lupien, Nitrini, & Caramelli, 2010). Moreover, elevated glucocorticoid levels have been found in the brains of patients with AD, although their role as a cause or effect of the disease process is unclear (Sotiropoulos et al., 2008). Plasma cortisol levels have been associated with cognitive impairments and more rapid disease progression in patients with AD (Csernansky et al., 2006; Huang, Lui, Chang, Lu, Wang, & Chang, 2009). However, other investigators have failed to find a relationship between variables of HPA axis dysfunction and cognitive impairment (Köhler, Thomas, Lloyd, Barber, Almeida, & O'Brien, 2010; Souza-Talarico, Caramelli, Nitrini, & Chaves, 2008). Although relationship between HPA axis dysfunction, depression, and cognitive impairment in AD has not been fully clarified, it is possible that hippocampal degeneration caused by HPA dysregulation may make patients more susceptible to the development of the neuropathological correlates of AD (Wright & Persad, 2007).

Thus, HPA axis dysfunction may represent a critical link between depression, AD, and cognitive impairment.

The prevalence and unique nature of depression in AD has not gone unnoticed. In 2002, the National Institute for Mental Health (NIMH) assembled the Depression of Alzheimer's Disease Workgroup in an attempt to review the issue of depression in AD and to determine appropriate guidelines for future research in this area. The workgroup concluded that depression occurring within the course of AD differs from MDD as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR. As such, the disorder warrants its own provisional criteria to aid in the regulation of future research (Lee & Lyketsos, 2003). A helpful summary of the provisional criteria is provided in Table 1.

Table 1. Highlights of the Provisional Diagnostic Criteria for Depression of Alzheimer's Disease.

1. All criteria are met for dementia of Alzheimer type (DSM-IV-TR).
2. The provisional criteria require three or more symptoms of depression, instead of the five symptoms required for idiopathic major depression. The symptoms are as follows: depressed mood, decreased positive affect or pleasure in response to social contact and usual activities, social isolation or withdrawal, disruption in appetite, disruption in sleep, psychomotor changes, irritability, fatigue or loss of energy, feelings of worthlessness, hopelessness, or excessive or inappropriate guilt, and recurrent thoughts of death, suicidal ideation, plan, or attempt.
3. Criteria were added for the presence of irritability and for the presence of social isolation or withdrawal.
4. Criteria for loss of interest or pleasure were revised to reflect decreased positive affect or pleasure in response to social contact and usual activities.
5. The criteria do not require presence of symptoms nearly every day, as is the case for major depressive episode, while requiring the presence of symptoms during the same 2-week period.

Reproduced from Lee, H.B. & Lyketsos, C.G. (2003). Depression in Alzheimer's disease: Heterogeneity and related issues. *Biological Psychiatry, 54*, 353-362. doi:10.1016/S0006-3223(03)00543-2

The findings of Starkstein, Jorge, Mizrahi, and Robinson (2005) called attention to potential issues with the NIMH provisional criteria. For example, depressed AD patients in their sample experienced loss of interest significantly more frequently than did AD patients who were not depressed. The investigators contended that replacing "loss of interest" with

"decreased positive affect" in the provisional criteria may lead to oversight of a prominent clinical feature of depression in AD. In addition, Starkstein et al. (2005b) stressed the necessity of an explicit definition of the irritability criterion given that depression and irritability may be separate, but comorbid disorders in AD. Lastly, depressed AD patients had significantly higher scores on the Pathological Laughing and Crying Scale subscale for crying than non-depressed patients, suggesting that affective lability may be a significant clinical feature of depression in AD that was omitted from the provisional criteria. The authors noted that the significant presence of affective lability has not been consistently demonstrated, but asserted that affective lability is both a frequent feature of depression in AD and a potentially powerful marker of depression. Generally speaking, the relaxed symptom and temporal criteria may cast too wide a net, overcompensating for a traditionally under-diagnosed disorder. As evidenced by these criticisms of the provisional criteria and reiterated by Lee and Lyketsos (2003), validation studies are needed, and these criteria may require modification as more conclusive research emerges.

Correlates of Depression in AD

Clarification of the above issues in diagnosis is particularly important given that AD patients with either major or minor depression show significantly greater psychological, neurological, and functional impairments than their nondepressed counterparts. Starkstein et al. (2005b) found that these patients scored significantly higher on measures of apathy, irritability, anxiety, pathological affective crying, parkinsonism, and social dysfunction and significantly lower on a measure of activities of daily living. Of note, AD patients with major or minor depression scored significantly worse on the Functioning Independence Measure than the nondepressed AD group, but there was not a significant difference between scores in

the two depressed groups. This finding suggests that even mild symptoms of depression can cause functional impairment (Starkstein et al., 2005b). Moreover, Ross et al. (1998) found that depression severity is positively associated with functional impairments (i.e., activities of daily living), over and above other contributing factors like cognitive abilities and age. Starkstein et al. (2005b) also found that patients with major depression had more severe anxiety, apathy, delusions, and parkinsonism than patients with minor depression. This lends evidence to the theory that these psychopathological and neurological symptoms worsen with increased depression severity. The presence of depression in AD has also been associated with more rapid rate of disease progression, earlier institutionalization, and increased caregiver burden (Zubenko et al., 2003).

The Impact of Depression in AD on Cognition

Depression has also been shown to negatively impact cognition in both demented and non-demented old adults. In older, non-demented adults depression has been traditionally associated with impairments in memory, attention, confrontation naming, verbal fluency, visuospatial ability, processing speed, and executive functioning. The effortful-automatic hypothesis (Hasher & Zacks, 1979) has been proposed to account for the wide range of cognitive deficits seen in depressed patients. The hypothesis posits an inverse relationship between the effort required to complete a task and a depressed subject's performance on that task. In other words, the more effortful the task, the lower the depressed subject's score.

Not surprisingly, patients with comorbid AD and depression also evidence diminished cognitive abilities. Despite symptom overlap, patients with AD may be distinguished from depressed, non-demented patients by their neuropsychological profile. According to Wright and Persad (2007), although both groups will likely display

impairments in similar domains, what distinguishes the profile of patients with AD is *severity* of the impairment in these domains. Furthermore, the impairment in patients with AD likely reflects a true loss of ability, rather than the amount of effort required as seen in depressed patients without AD (Wright & Persad, 2007). Although both depressed and AD patients both show decrements in memory performance, it may be that executive dysfunction (i.e., difficulty organizing information and planning) is primarily responsible for impaired recall in depressed patients. Moreover, depressed patients tend to retain learned material over time. On the other hand, patients with AD show a faster rate of forgetting initially recalled material over time, impairment in memory consolidation as measured by recognition memory tasks, and a greater number of false-positive errors. Moreover, AD patients display deficits in temporal orientation, praxis, and visuoperceptual functions not typically observed in depressed, non-demented patients (Wright & Persad, 2007).

The cognitive implications of depression in AD have been studied extensively without consistent results. In addition to the issues inherent in diagnosing depression in AD, methodological flaws and inconsistencies underlie the contradictory findings and have fueled the debate surrounding this topic. For example, some studies have not controlled for AD severity. In other cases, only the Mini-Mental State Examination (MMSE) was used as an outcome variable to represent cognitive functioning. These studies thereby report cognitive impairment as decreased MMSE scores that are also sensitive to AD progression (Fahlander, Berger, Wahlin, & Bäckman, 1999).

Wefel, Hoyt, and Massman (1999) divided a sample of 135 participants with mild or moderate probable AD into a depressed group and non-depressed control group based on Geriatric Depression Scale (GDS; Brink et al., 1982) score cut-offs. They compared the

performance of these two groups on a comprehensive neuropsychological battery, expecting differences on verbal timed tests, visuospatial time-limited tests, tests of attention and concentration, and speeded motor tests. The AD group with depression performed significantly worse on WAIS-R Block Design and Digit Span forwards and the Halstead-Reitan Finger Tapping Test. They also performed more poorly than the control group on WAIS-R Object Assembly, Picture Arrangement, Digit Span backwards, and a measure of phonemic fluency, although these differences did not quite reach statistical significance.

Starkstein et al. (2005b) analyzed the performance of mild and moderate AD patients on six neuropsychological measures: WAIS-III Digit Span Forwards, Digit Span Backwards, and Block Design, Boston Naming Test, Controlled Oral Word Association, and Buschke Selective Reminding Test (Delayed Recall). A two-way ANCOVA comparing the major, minor and nondepressed groups on 6 cognitive tests (using MMSE score as a covariate) showed a significant overall effect. Post-hoc analyses revealed a significant difference between the group with major depression and the nondepressed group only on Block Design performance. Other authors have found that AD patients with depression obtain significantly lower scores on the MMSE (Rovner, Broadhead, Spencer, Carson, & Folstein, 1989), full scale IQ (Breen, Larson, Reifler, Vitaliano, & Lawrence, 1984), and measures of dementia severity, working memory, and processing speed (Rubin, Kinscherf, Grant, & Storandt, 1991) than AD patients without depression.

A few authors have found no cognitive differences between AD patients with and without depressive symptoms. Lopez, Boller, Becker, Miller, and Reynolds (1990) compared the neuropsychological test performance of AD patients with and without a diagnosis of MDD. They found no significant differences at baseline or at one-year follow-up on

measures of memory, expressive and receptive language, visuospatial ability, speed and attention. Moreover, they found no difference in the rate of cognitive decline over one year (as measured by the MMSE). Of note, the study sample size was small and the researchers used composite scores to represent cognitive level. Fahlander et al. (1999) found no significant differences in free recall, recognition, or immediate memory span between a group of patients with AD only and a group with AD and depression. These investigators ultimately concluded that depression is eclipsed by the neurodegenerative process in AD and exerts little, if any, effect on memory performance.

Apathy in AD: Definition and Prevalence

Like depression, apathy is one of the most prevalent behavioral correlates of AD, and is perhaps the most common of all (Drijgers, Verhey, Leentjens, Köhler, & Aalten, 2011). Unfortunately, it is a syndrome far less frequently studied than is depression in AD. As defined by Tagariello, Girardi, and Amore (2009), apathy is diminished motivation not attributable to impaired consciousness, cognition, or behavioral distress. In other words, it is a form of executive dysfunction, characterized by diminished initiation and persistence, lack of interest, indifference, decreased social engagement, blunted emotional responsiveness, and lack of insight (Landes, Sperry, Strauss, & Geldmacher, 2001). With increasing evidence of the prevalence and importance of apathy in AD, a task force with members from the European Psychiatric Association and European Alzheimer's Disease Consortium developed diagnostic criteria for apathy in AD, which may be found in Table 2 (Robert et al., 2009). These criteria largely reflect those adapted from Marin (1991) by Starkstein et al. (2001) in their inclusion of the three domains of apathy and their exclusionary criteria.

Table 2. Diagnostic Criteria for Apathy in AD

For a diagnosis of apathy, the patient should fulfill criteria A, B, C, and D.

A. Loss of, or diminished, motivation in comparison to the patient's previous level of functioning and which is not consistent with his/her age or culture. These changes in motivation may be reported by the patient or by the observations of others.
B. Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time:
    a. Behavior: Loss of, or diminished, goal-directed behavior as evidenced by at least one of the following:
        i. Initiation symptom: Loss of self-initiated behavior (e.g., starting conversation, doing basic tasks or day-to-day living, seeking social activities, communicating choices);
        ii. Responsiveness symptom: Loss of environment-stimulated behavior (e.g., responding to conversation, participating in social activities).
    b. Cognition: Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:
        i. Initiation symptom: Loss of spontaneous ideas and curiosity for routine and new events (e.g., challenging tasks, recent news, social opportunities, personal/family and social affairs);
        ii. Responsiveness symptom: Loss of environment-stimulated ideas and curiosity for routine and new events (e.g., in the person's residence, neighborhood, or community).
    c. Emotion: Loss of, or diminished, emotion as evidenced by at least one of the following:
        i. Initiation symptom: Loss of spontaneous emotion, observed or self-reported (e.g., subjective feeling of weak or absent emotions, or observation by others of a blunted affect);
        ii. Responsiveness symptom: Loss of emotional responsiveness to positive or negative stimuli or events (e.g., observer reports of unchanging affect or of little emotional reaction to exciting events, personal loss, serious illness, emotionally-laden news).
C. The symptoms in criteria A and B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to a diminished level of consciousness or the direct physiological effects of a substance (e.g., a drug of abuse, a medication).

Reproduced from Robert, P.H., Mulin, E., Malléa, P., & David, R. (2010). Apathy diagnosis, assessment, and treatment in Alzheimer's Disease. *CNS Neuroscience & Therapeutics, 16*, 263-271.

According to Starkstein, Jorge, and Mizrahi (2006a), prevalence estimates of apathy in AD range from 19-76%. As with depression in AD, this broad range may be explained by variability in the definition of and methods used to assess apathy in AD. Results from some previous studies have suggested that apathy may be more common in men than in women with AD (Ott, Tate, Gordon, & Heindel, 1996), but this proposed relationship between apathy and gender remains controversial (Landes et al., 2001).

The literature suggests that apathy may be an even more common behavioral syndrome than is depression in AD. Landes, Sperry, and Strauss (2005) used the Dementia

Apathy Interview and Rating (a structured caregiver interview), Blessed Rating Scale for Dementia (BRSD), and DSM-IV to assess the prevalence and frequency of apathy, dysphoria, and MDD in patients with possible and probable AD. Approximately 68% of the sample experienced symptoms of dysphoria fewer than 1-2 days in the previous month. On the other hand, 59% of patients experienced symptoms of apathy at least 4-8 days in the preceding month. Although a greater percentage of female patients experienced depressive symptoms, the proportions of men and women who experienced apathy were approximately equal. The investigators then created high and low frequency categories for each set of symptoms, with high frequency defined as greater than 1-2 times per week and low frequency defined as less than 1-2 times per week. Far more caregivers reported patients experiencing high frequency apathy (n = 78) than high frequency symptoms of dysphoria (n = 11). Moreover, it appears that the symptoms and severity of apathy only increase with the severity of AD. Unlike the course of depression in AD, the findings regarding the course of apathy in AD show that apathy often appears early in the disease and its frequency increases with AD severity and illness duration (Devanand et al., 1992; Gilley, Wilson, Bennett, Bernard, & Fox, 1991; Iulio, et al., 2010; Landes et al., 2005; Mega et al., 1996). This data suggests that apathy is at least as frequent and problematic as is depression within the context of AD.

Distinguishing Depression from Apathy

As noted above, apathy is often difficult to distinguish from depression in the context of dementia, due to frequent comorbidity and symptom overlap (Landes et al., 2001). First, apathy must also be distinguished from loss of ability due to cognitive or functional decline in the context of AD (Landes et al., 2001; Tagariello et al., 2009). Then, apathy must be

distinguished from depression in the likely presence of symptom overlap. In particular, loss of interest is a key symptom in both syndromes. In the Landes et al. (2005) study referenced above, 73% of those patients who met DSM-IV criteria for MDD reported loss of interest. However, it may be that loss of interest more accurately reflects loss of motivation, rather than an affective disorder. Differentiating between a motivational and affective cause of interest loss may be critical in distinguishing apathy from depression.

Table 3. Differences and Overlap in the Clinical Symptoms of Apathy and Depression.

Symptoms of Apathy	Symptoms Common to Apathy and Depression	Symptoms of Depression
Blunted emotional response Indifference Low social engagement Diminished initiation Poor persistence	Diminished interest Psychomotor retardation Fatigue/hypersomnia Lack of insight	Dysphoria Suicidal ideation Self-criticism Guilty feelings Pessimism Hopelessness

Reproduced from Landes, Sperry, Strauss, & Geldmacher. (2001). Apathy in Alzheimer's disease. *Journal of the American Geriatrics Society*, *49*, 1700-1707.

Mounting evidence suggests that apathy is a distinct neuropsychiatric syndrome that warrants further study (Tagariello et al., 2009). Although the symptoms of depression and apathy overlap, certain symptoms help to differentiate between them (see Table 3). In particular, apathy is associated with a blunted emotional response, thereby negating symptoms of depression like sad mood and feelings of guilt, helplessness, and hopelessness. Instead, apathy is associated with the vegetative symptoms of depression (e.g. psychomotor retardation, fatigue, hypersomnia, lack of insight, and pessimism). The two syndromes may also be distinguished by their associations with different neuropsychiatric symptoms. For example, depression is commonly accompanied by irritability, anxiety, agitation, and hallucinations. Apathy, on the other hand, most frequently co-occurs with disinhibition and aberrant motor behavior (Tagariello et al., 2009).

Results from the Cache County Study on Memory Health and Aging demonstrate that nearly half of AD patients with apathy do not evidence comorbid depression. Similarly, Starkstein, Petracca, Chemerinski, and Kremer (2001) found that AD patients with apathy only and patients with neither apathy nor depression had similar total scores on Hamilton Depression Rating Scale, bolstering the theory that apathy and depression are distinct disorders in AD. Moreover, rates of comorbidity vary across neurological disorders (Landes et al., 2001), suggesting that depression and apathy are not simply different behavioral manifestations of a common neuropathological process. Lastly, for patients whose depression was treated with SSRIs or haloperidol, symptoms of depression decreased, but apathy worsened (Landes et al., 2001). These results bolster the hypothesis that depression and apathy represent distinct neuropathological processes. Of note, the prevalence of apathy and the symptom overlap between apathy and depression may contribute to misdiagnosis and overestimation of depression prevalence in AD.

Neurobiological differences also help to distinguish apathy from depression in AD. Apathy is associated with neuronal loss, higher tangle counts, and white matter hyperintensities in components of the frontal-subcortical circuit (Landes et al., 2001). Also associated with apathy are neuronal loss in the nucleus basalis of Meynert and hippocampus, and tangles in the medial frontal lobe, parahippocampal gyrus, and parietal lobe (Landes et al., 2001). SPECT studies have shown apathy to be related to significant hypoperfusion in anterior temporal, orbito-frontal, anterior cingulate, DLPFC regions (Cummings, 2000), and right posterior tempoparietal cortex (Ott, Noto, & Fogel, 1996).

Although both depression and apathy involve the frontal-striatal and subcortical limbic circuits, the neurotransmitters involved distinguish the two syndromes. As stated

above, depression is primarily associated with either serotonergic deficits or an imbalance between dopamine and norepinephrine. Apathy, on the other hand, is associated with cholinergic deficits, specifically a loss of cholinergic input to prefrontal and subcortical structures from the nucleus basalis of Meynert (Tagariello et al., 2009). This theory is bolstered by evidence showing that apathy decreases in patients given a cholinesterase inhibitor (Wynn & Cummings, 2004). Although initial findings were inconsistent, more recent studies suggest that a variety of cholinesterase inhibitors are beneficial in reducing symptoms of apathy in patients with AD, including donepezil, galantamine, and rivastigmine (Malloy & Boyle, 2005). This association with cholinergic deficits may explain why the frequency and severity of apathy increases as AD progresses, if both processes reflect the same underlying cholinergic deprivation. The similar neuroanatomical, but different neurochemical bases for apathy and depression are important to understand, as the treatment of depression may exacerbate symptoms of apathy (e.g., treatment with SSRIs; Tagariello et al., 2009).

Despite these differences, the correlates of apathy in AD are similar to those of depression in AD. For example, AD patients with apathy demonstrate greater cognitive and functional impairment, illness duration, decreased quality of life, and earlier institutionalization (Tagariello et al., 2009). Even after controlling for depression and severity of cognitive impairment, Boyle and Mailey (2004) found that apathy was associated with more severe impairments in activities of daily living. Not surprisingly then, apathy in AD is also associated with increased dependency and caregiver burden (Landes et al., 2001). Apathy in AD has also been shown to be associated with more severe extrapyramidal signs (Starkstein et al., 2001) and significantly higher rates of depression and dysthymia (Kuzis,

Sabe, Tiberti, Dorrego, Starkstein, 1999). In light of the evidence enumerated above, Tagariello et al. (2009) suggested that apathy may represent a behavioral manifestation of a more "aggressive" form of AD, characterized by more severe behavioral problems and more rapid decline of cognitive, functional, and emotional capabilities.

The Impact of Apathy in AD on Cognition

Evidence from several studies suggests that apathy is associated with cognitive impairment in multiple domains, as well as functional impairment (Devanand et al., 1992; Hall, O'Bryant, Johnson, & Barber, 2011; Landes et al., 2001; Paulsen et al., 1996; Sperry, Strauss, & Landes, 2001). Investigators have also suggested that apathy may contribute to cognitive impairment more significantly than does depression in AD (Drijgers et al., 2011; Kuzis et al., 1999; Landes et al., 2005). Landes et al. (2005) used the DSM-IV, Dementia Apathy Interview and Rating, MMSE, Clinical Dementia Rating (CDR), and Blessed Dementia Rating Scale (BDRS) to assess the relationship between dysphoria, apathy, cognition, AD severity, and functional ability. First, they found that apathy increased across stages of dementia (r = .47). Their measure of apathy frequency was also significantly negatively related to MMSE score (r = -.36) and positively related to functional impairment (r = .56). Frequency of dysphoria was not significantly correlated with CDR or MMSE scores; however, it was related to BDRS activities of daily living scores (r = .21).

Kuzis et al. (1999) investigated the unique and combined impact of depression and apathy on cognitive abilities. Participants in this study were 133 patients who met NINCDS-ADRDA criteria for probable AD and 51 patients who met criteria for mild cognitive impairment. Patients underwent a psychiatric evaluation that included the SCID, HAM-D, and the Apathy Scale. Diagnosis of depression was based on DSM-IV criteria, and patients

were considered apathetic if they scored 2 SD above the mean on the Apathy Scale. On the basis of these evaluations, patients were classified into one of four categories: 1) depression or dysthymia without apathy, 2) apathy without depression, 3) both depression and apathy, and 4) neither apathy nor depression.

Patients were also administered a comprehensive neuropsychological battery. For patients with apathy only, scores on Buschke total recall and the Boston Naming Test were significantly worse than for all other groups tested, and scores on Buschke delayed recall were significantly worse than those of patients with depression only. Patients with apathy performed significantly worse than patients without apathy on the Wisconsin Card Sorting Test and FAS (a measure of verbal fluency). Only on Raven's Matrices did depression contribute to impairment over and above apathy alone, as patients with both depression *and* apathy performed significantly worse than all other groups. Of note, no significant differences between the depression only group and the control group were found on any neuropsychological test. In addition, depression in AD did not contribute to cognitive deficits in AD above and beyond the disease process itself.

Sperry et al. (2001) also found that apathy scores were significantly related to impaired functional capacity, increased disease severity, and impaired performance on measures of verbal fluency, confrontation naming, word list learning, and the MMSE. Depressive symptoms were not significantly related to cognitive or functional capacity or AD severity. Even after controlling for depressive symptomatology, the relationship between apathy scores and the aforementioned variables did not change. Ultimately, it appears that symptoms of apathy in AD have a stronger and more consistent relationship with the progression of cognitive and functional decline in AD than do symptoms of depression.

The potential behavioral, psychological, neurological, and cognitive correlates of depression and apathy in AD necessitate effective and early diagnosis, even in the face of a complicated diagnostic picture. Unfortunately, the study of apathy is relatively recent, and few diagnostic scales exist. The Apathy Scale (Starkstein et al., 1995), Dementia Apathy Interview and Rating (Strauss & Sperry, 2002), Apathy Evaluation Scale (AES; Marin, Biedryzcki, & Firinciogullari, 1991), Neuropsychiatric Inventory (Cummings et al., 1994), Lille Apathy Rating Scale (Sockeel et al., 2006), Structured Clinical Interview for Apathy (Starkstein, Ingram, Garau, & Mizrahi, 2005), and Apathy Inventory (Robert et al., 2002) are all options that have been validated in various populations and used in research. As the evidence for apathy as a common and problematic syndrome mounts, these scales will undoubtedly become more widely used in clinical practice. Until that time, it may be wise to utilize other tools already common in clinical practice to assess symptoms of apathy. Although the Geriatric Depression Scale (GDS) was designed to measure symptoms of depression in older adults, there is evidence that the GDS is actually a multi-factorial instrument assessing symptoms of both dysphoria and apathy.

The Geriatric Depression Scale

The GDS (Brink et al., 1982) was designed explicitly to screen for depression in elderly people (Yesavage et al., 1983). To that end, its creators used a yes/no format to eliminate confusion potentially caused by Likert-scale response options. The GDS also eliminated questions regarding somatic symptoms, due to the fact that disease or normal aging may be responsible for somatic complaints in a geriatric population (Adams, 2001). With these purposeful changes, the GDS has been shown to be reliable, valid, sensitive, and specific in the identification of depression in older adults. Kieffer and Reese (2002)

determined the reliability of the GDS across 338 existing studies to be .848 (SD = .087). Bentz and Hall (2008) used discriminant function analyses to determine the ability of the GDS to predict DSM-IV depression diagnosis. They found the sensitivity of the GDS to be 82.6% and its specificity 81.3%. Additionally, their analyses suggested that the GDS is superior to the Beck Depression Inventory (BDI) in its ability to classify depression in a geriatric inpatient population. The purposeful design and demonstrated reliability, internal consistency (Adams, 2001; Parmelee, 1989; Yesavage, 1983), and validity (Abraham, Wofford, Lichtenberg, & Holroyd, 1994; Montorio & Izal, 1996; Sheikh, Yesavage, Brooks, Friedman, & Gratzinger, 1991) of the GDS have helped it to gain prominence in clinical practice and gerontology research (Adams, Matto, & Sanders, 2004).

Despite its popularity and continued use, the GDS is not without its critics. On occasion, the GDS has been found to have questionable sensitivity (Parmelee et al., 1989), specificity (Blazer, 2003), or both (Adams, 2001). Perhaps even more important is the debate that concerns its applicability in the cognitively impaired elderly. Given the prevalence of dementia in older adults, it is critical to determine whether a scale designed specifically to assess depression in older adults is capable of doing so accurately in the presence of cognitive decline. Mast (2005) found that the internal reliability of the GDS did not decline as a function of dementia severity (.86 in mild and .88 in severe dementia). Parmelee et al. (1989) compared standardized alpha coefficients for those participants with scores in the cognitively impaired range on the Blessed-Dementia Information-Memory-Concentration Test with those who were deemed cognitively intact and found that they were essentially identical (.92 impaired, .91 intact). There was also similar agreement for the GDS with depression diagnoses based on a checklist and DSM-III-R criteria for the presence or absence

of depression for both groups. There were no significant differences in false negative or false positive rates between the groups. Based on these findings, the authors concluded that the GDS may be reliably used to assess depressive symptoms in mildly and moderately cognitively impaired patients. Other investigators have found a notable inverse relationship between cognitive impairment and GDS reliability (Burke, Houston, Boust, & Roccaforte, 1989; Debruyne et al., 2009; Gilley & Wilson, 1997; Kørner et al., 2006; Lam et al., 2004; Müller-Thomson et al., 2005). Due to methodological issues and study design discrepancies, the literature on this topic remains equivocal.

Given the popularity of the GDS in research and clinical practice, it would be helpful to know whether or not the GDS could be used to identify both apathy and depression in patients with probable AD. Several previous factor analytic studies have found that the GDS is comprised of separate dysphoria and apathy/withdrawal factors. The identification and differentiation of depression and apathy will allow a proper analysis of the relationship of these behavioral correlates to cognitive impairment, functional impairment, and other clinical outcomes. This information will have practical implications for improving patient care and quality of life in both patients and their caregivers.

Factor Structure of the Geriatric Depression Scale

Parmalee, Lawton, and Katz (1989) were the first group of authors to perform a principal components analysis (PCA) on the GDS. Their sample was drawn from a population of elderly persons living in a multilevel-care nursing home and congregate apartment complex at the same site. Participants were excluded if they were too cognitively impaired to respond to questions, had speech or hearing deficits that prevented their completion of the interview, or were too ill to endure a lengthy interview.

Parmalee et al. (1989) included 417 complete GDSs in their unconstrained principal components analysis. This analysis with oblique rotation yielded six components with eigenvalues greater than 1. Together, these six components accounted for 52.3% of the total variance. The factors were named Dysphoria (14 items), Worry (4 items), Withdrawal/Apathy (4 items), Vigor (3 items), Decreased Concentration (2 items), and Anxiety (3 items). The components were generally weakly correlated, but the first component, Dysphoria, showed the strongest associations with the others. The Dysphoria component accounted for 29.9% of the variance alone, leading the authors to conclude that the scale is largely one-dimensional and is most clinically useful as a total score.

The authors themselves note the weaknesses in their study. Although the components extracted in this study clearly reflect dimensions of depression that have since been replicated, the criteria for inclusion in the sample are vague, at best. Authors did not exclude participants for severe cognitive impairment on any reliable measure or discuss the cognitive characteristics of the participants included. Moreover, they did not include any information about dementia diagnoses of any type. Although the age range of the participants whose GDS data were included in the PCA was not noted, the total sample ranged from 61 to 91 years (mean = 83.8 years). Given the prevalence of dementia in this age group, it is reasonable to assume that a fair number may have been classified as demented and not met the study's cognitive criterion for exclusion. In any case, this mixed cognitive sample cannot be an adequate representation of GDS responses in patients with AD.

Sheikh et al. (1991) also performed a PCA with varimax rotation on a sample of 326 elderly subjects ranging in age from 66 to 92 years. No mention was made of exclusion criteria for the study. The authors chose to retain five components with eigenvalues greater

than one, yielding a structure that accounted for 42.9% of the total variance. They described the components as sad mood, lack of energy, positive mood, agitation, and social withdrawal. While their components have face validity, their failure to delineate inclusion criteria makes this factor structure questionable if applied to patients with AD.

Salamero and Marcos (1992) were the next authors to explore the factor structure of the GDS. They, too, conducted a PCA on a sample of 234 adults between the ages of 60 and 95. Subjects were included solely on the basis of their willingness to participate; no inclusions or exclusion criteria was enacted on the basis of psychopathology or physical health. This initial analysis gave rise to 9 components which accounted for 59% of the total variance. Salamero and Marcos (1992) opted to test oblique and varimax rotations on different numbers of components. The results were always similar, and they ultimately concluded that only the first three components were clinically interpretable. They related them to depressed mood, cognitive impairment, and withdrawal/avoidance, but noted that some incompatible items within these components made interpretation difficult. As in the analyses by Parmelee, Lawton and Katz (1989) before them, the authors suggested that the GDS is largely unidimensional.

Even a brief glance at component distributions and loadings does reveal significant scatter and low item loadings. Salamero and Marcos (1992) concluded that the factorial analysis was substandard. Unfortunately, as their ultimate goal was to relate the factor structure of the GDS to the structure and symptoms of Beck's cognitive model of depression, they paid little attention to their sample's demographics and diagnoses. No mention of exclusionary criteria was made, even to control for cognitive impairment that might have rendered the results of the GDS invalid. There was no breakdown of the sample on any

measure of global cognition or any screening for physical illness or dementia. With this in mind, it is difficult to imagine a population to which this factor structure might apply or in which it might clarify the unique dimensions of depression.

Abraham et al. (1994) examined the factor structure of the GDS in a sample of depressed nursing home residents. Subjects who showed signs of depression were recruited from seven nursing homes. Participants displayed a wide range of cognitive functioning (MMSE scores ranged from 4 to 30). The investigators conducted a principal components analysis with varimax rotation on 917 complete GDSs and obtained a six-component solution which accounted for 55.1% of the total variance. All retained eigenvalues were greater than 1. The resulting components were Life Dissatisfaction (6 items), Dysphoria (6 items), Hopelessness/Decreased Self-Attitude (5 items), Rumination/Anxiety (5 items), Social Withdrawal/Decreased Motivation (3 items), and Decreased Cognition (5 items). Of note, the PCA yielded four items with loadings < .40, three of which loaded onto the sixth component, Decreased Cognition. The investigators noted that the four items in question (Do you find life very exciting? Do you feel full of energy?, Are you hopeful about the future?, and Do you think it is wonderful to be alive now?) target themes with limited relevance for older persons residing in nursing homes. In fact, the pervasiveness of those symptoms and their endorsement by members of this sample may explain their low factor loadings.

Adams (2001) conducted a principal components analysis on the GDS after it was mailed to and completed by 272 members of a health maintenance organization who were at least 65 years of age. Members were randomly selected for mailings after those with AD, other dementias, mental retardation, and schizophrenia had been screened out. The PCA yielded 9 components with eigenvalues greater than 1, but Cattell's scree plot suggested 6

final factors that accounted for 50.4% of the total variance. Factors 1 and 5 both dealt with depressed mood, and so were named Dysphoria 1 and 2, respectively. Factor 2 was named Withdrawal/Apathy and Vigor (WAV) as it comprised six of the seven items of the Withdrawal/Apathy and Vigor factors found previously by Parmelee, et al. (1989). The remaining factors contained items that pertain to and were named Anxiety, Mental Impairment, and Agitation.

The WAV factor was of particular interest to Adams (2001). She found that all six of the WAV items from her PCA and the remaining item grouped with these items by Parmelee et al. were the seven most endorsed items in their sample. Moreover, only 24.8% of the sample failed to endorse an item on the WAV scale. Adams (2001) investigated further to determine the particular contribution of the items in this factor to GDS total scores and depression classification. Using a GDS cut-off score of 11 points, removing WAV items and prorating total scores, she found that 8.1% of this new, prorated sample would have been classified as depressed, compared to 12.9% of the original sample. In other words, the WAV items were responsible for 13 of the 35 original depression diagnoses in the sample. These analyses suggest that these items are disproportionately experienced by older, non-demented, community-dwelling adults. It is also important to note that differences in endorsement rates and mean subscale scores between the WAV component and combined Dysphoria components lends evidence to the hypothesis that certain symptoms of apathy are experienced more frequently than the dysphoric symptoms typically associated with depression. Adams suggested that these WAV items may better reflect depletion or disengagement conditions than they do depression. Of note, this sample screened out AD and other dementias, so her findings may not be applicable in an AD population.

Bentz and Hall (2008) used a PCA to compare the factor structure of the GDS to the BDI and to examine their respective abilities to accurately classify depression in a geriatric population. Investigators conducted a retrospective chart review of 158 patients admitted to a geriatric psychiatry inpatient unit. Subjects were included on the basis of their age (greater than 64 years) and completion of psychological and neuropsychological testing. Diagnoses were made based on DSM-IV criteria, and investigators collapsed diagnoses of Major Depressive disorder, Dysthymic disorder, and Depression NOS into a single "depression" category. Similarly, diagnoses of Dementia of the Alzheimer's type, Dementia due to a general medical condition, and Dementia NOS were classified as "dementia." However, these diagnoses were not utilized as inclusion or exclusion criteria. Ultimately, 27.7% of the patients in the final sample were classified as only demented, 15.8% were classified as only depressed, and 53.8% of patients in the final sample met criteria for both depression and dementia. Patients were administered a battery of neuropsychological measures (CERAD) that includes the MMSE as well as measures of verbal fluency, confrontational naming, constructional abilities, immediate and delayed verbal memory, and verbal memory recognition. An additional measure of orientation was included. Patients also completed both the BDI and GDS.

The authors conducted their principal components analysis on both the BDI and GDS with varimax rotation. They limited their resulting components to those with at least three items with sufficient loadings and eigenvalues greater than one. This analysis yielded five initial factors that were eliminated due to fewer than three items loading, leaving five meaningful factors that accounted for 44.4% of the common variance. The components were

named Hopelessness (7 items), Social Isolation (3 items), Negative Affect (5 items), Irritability (3 items), and Worry (3 items).

The authors then used total and factor scores from both the BDI and GDS in correlational analyses with the neuropsychological measures described above. None of the components of the GDS were found to correlate significantly with any of the neuropsychological measures. Once again, the nonspecific nature of the groups in this sample prohibits definitive conclusions about the relationship between GDS factors and cognitive impairment in AD.

Hall and Davis (2010) explored the factor structure of the GDS in a sample of older adults diagnosed with some level of cognitive impairment (based on a battery of neuropsychological tests for the assessment of dementia). Participants were community-dwelling adults older than 58 years of age. Diagnoses included AD, Vascular dementia, and Cognitive Disorder NOS, but 40 patients were classified as either "Other," "Mixed," or "None." Twenty-three patients in the final sample underwent second or third evaluations, conducted approximately one year after previous evaluations. However, the authors noted that consecutive administrations were deemed suitably independent to be included in the analyses. After eliminating patients with MMSE scores below 15 to ensure self-report capabilities, 173 GDSs were included in the PCA.

The factor analysis originally yielded nine eigenvalues greater than one. However, Cattell's scree plot suggested a final solution with four components that explained 38.3% of the total variance. The authors named the factors Dysphoria (11 items), Meaninglessness (7 items), Apathy (6 items), and Cognitive Impairment (6 items). Four items had factor loadings < .40. As in previous studies, only Cognitive Impairment had questionable

reliability, with an alpha coefficient equal to .468. Hall and Davis (2010) also presented data from the zero-order correlation among the four factors. As might be expected, there was a significant association between the Dysphoria and Meaninglessness factors. Apathy had low correlations with each of the other factors, and Cognitive Impairment had the lowest absolute correlations with Dysphoria (r = .008) and Meaninglessness (r = .001).

Although Hall and Davis (2010) did not relate these four components to performance on neuropsychological measures, Hall et al. (2011) did so in a sample of 272 patients with mild AD and 356 cognitively normal controls. In the patients with AD, the Dysphoria factor was associated with worse performance on FAS, Trail Making Test A and B, and Digit Span. The Apathy factor was significantly related to performance on Logical Memory I and II. The authors took their analyses one step further and re-ran their data separately for men and women. In women with AD, apathy was significantly related to performance on FAS, Logical Memory II and Visual Reproduction I. Dysphoria was significantly related to performance on Trail Making Test A and B. In men with AD, the only significant relationship was between the Dysphoria factor and performance on Digit Span. The authors concluded that symptoms of apathy and dysphoria may impact performance in certain cognitive domains and that the relationship may be influenced by gender. Of note, the depressive symptom clusters used by Hall et al. (2011) were those taken from Hall and Davis' (2010) PCA, performed on a sample of patients with cognitive impairment of various severity and etiology. The application of these components to a sample of patients with mild AD is of questionable validity.

Adams et al. (2004) appears to be the only confirmatory factor analysis of the GDS to date. Adams and her colleagues applied data from 294 older adults in either independent-

living retirement facilities or assisted living to the factor structure obtained in Adams' 2001 PCA. They used a tetrachoric transformation of the covariance matrix prior to estimation of the measurement model and chose to employ the chi-square test, goodness-of-fit index (GFI), adjusted GFI (AGFI), and standardized root mean square residual as fit indices for both a full model and alternative nested models.

Adams et al. (2004) analyzed the full six-factor model derived to determine its fit with the current sample. The standardized validity coefficients ranged from .40 to .64 for the Dysphoric Mood factor, from .45 to .55 for the WAV factor, from .48 to .54 for the Anxiety factor, from .30 to.55 for the Mental Impairment factor, and from .46 to .60 for the Hopelessness factor. The three-item Agitation factor did not obtain any standardized lambda coefficients greater than .40. The chi-square test was significant ($p = .015$), meaning that the data did not fit the original model. The full model's GFI was .88 and standardized root mean square residual was .055, both of which were close to the recommended criteria for goodness of fit.

After this initial analysis, Adams et al. (2004) tested alternative models. The first alternative model eliminated the unreliable and ill-fitting Agitation factor and Item 14 ("Do you have more memory problems than most?"), which showed the lowest item validity ($\lambda = .30$). This five-factor and 26-item model showed similar validity coefficients, but a slight improvement on each of the fit indices. Adams et al. (2004) then tested two other alternative models, first collapsing the Dysphoria 1, Dysphoria 2 (Hopelessness), and Anxiety factors into a single factor and included the WAV, Mental Impairment, and Agitation factors. The third model was identical to the second, but removed the Agitation factor. The chi-square differences for these two alternative models did not show any significant improvement over

the first alternative, and the authors suggested that collapsing the mood items sacrificed some conceptual meaning in the model. Ultimately, they decided to use the first alternative model for the remaining analyses.

Of note are the similarities in the components extracted in these previous studies. First, there is consistently a dysphoria component or a synonymous component. There is also frequently a component that represents symptoms of apathy, or symptoms related to apathy (e.g., diminished motivation or social withdrawal). Several studies also had dimensions related to cognitive impairment and anxiety or worry (Adams et al., 2004). Table 4 provides a brief summary of the existing studies as described above.

In reviewing these studies, it is important to note several common methodological choices on which I intend to improve. First, all of the aforementioned studies used principal components analysis, with the exception of Adams' (2004) confirmatory factor analysis. These previous studies also used samples of cognitively intact or heterogeneously impaired subjects, or failed to describe the cognitive characteristics of the sample. In the case of Sheikh et al. (1991) and Salamero and Marcos (1992), the authors provide only an inclusive age range. Given that their samples comprised elderly subjects, it is safe to assume that some subjects were experiencing a degree of cognitive impairment, potentially rendering the GDS responses invalid. In the case of Abraham et al. (1992) and Bentz and Hall (2008), subjects were recruited on the basis of a psychiatric diagnosis (e.g., depression), rather than a cognitive one. Adams (2001) actually excluded participants with dementia. Finally, Hall and Davis (2010) included subjects with cognitive impairment and effectively described the cognitive characteristics of their sample. However, their sample included patients with heterogeneous cognitive impairments (diagnoses included AD, Vascular dementia, Cognitive

Disorder NOS, and patients classified as either "Other," "Mixed," or "None"). Ultimately, though, it seems reasonable to conclude that none of these studies produced results that can be appropriately applied to patients with pure Probable AD. In addition, only one previous factor analytic study related the structure of the GDS to cognitive impairment by examining subjects' performance on neuropsychological testing. Ultimately, none of the existing studies have used exploratory factor analysis to explicitly examine the factor structure of the GDS in a large, pure sample of probable AD patients and then related that factor structure to performance on neuropsychological measures.

Table 4. Summary of Previous PCA Samples and Findings

Authors	Analysis	N	Sample description	# of Components	Component Names
Parmalee, Lawton, and Katz (1989)	PCA	417	"not too cognitively impaired" elderly	6	Dysphoria, Worry, Withdrawal/Apathy, Decreased Concentration, Anxiety
Sheikh et al. (1991)	PCA	326	Ages 66-72	5	Sad mood, Lack of energy, Positive mood, Agitation, Social Withdrawal
Salamero and Marcos (1992)	PCA	234	Ages 60-95	3	Depressed mood, Cognitive impairment, Withdrawal/Avoidance
Abraham et al. (1992)	PCA	917	Depressed nursing home residents	6	Life dissatisfaction, Dysphoria, Hopelessness, Anxiety, Social withdrawal/Decreased motivation, Decreased cognition
Adams (2001)	PCA	271	Community-dwelling, Age > 65, no dementia, MR, or schizophrenia	6	Dysphoria 1 and 2, Withdrawal/Apathy, Vigor, Anxiety, Mental impairment, Agitation
Bentz and Hall (2008)	PCA	158	Geriatric inpatient psychiatric unit, Age > 64	5	Hopelessness, Social Isolation, Negative Affect, Irritability, Worry
Hall and Davis (2010)	PCA	173	Community-dwelling, Cognitive impairment (AD, VD, CD NOS, Other, Mixed, None)	4	Dysphoria, Meaninglessness, Apathy, Cognitive Impairment

MR = mental retardation, VD = Vascular dementia, CD NOS = Cognitive Disorder, Not Otherwise Specified

With this in mind, I plan to perform an exploratory factor analysis of the Geriatric Depression Scale in a large sample of probable AD patients (with mild-to-moderate dementia) with comprehensive diagnostic evaluations and a thorough neuropsychological assessment. The experimental hypotheses are:

1. An apathy factor of the GDS will emerge more strongly in this sample of pure AD patients than it has in other studies with mixed samples of cognitively impaired adults or healthy elderly adults.
2. Based on the somewhat limited literature on the relationship between apathy and cognitive impairment in AD, I expect the apathy factor score to significantly predict patients' performances on measures of phonemic fluency, motor speed, processing speed, verbal memory, and confrontation naming, even when the dysphoria factor score is taken into account. In order to broaden the knowledge base about this topic, I will also investigate the relationship between apathy scores and other neuropsychological variables yet unstudied.
3. A dysphoria factor will emerge, but will not significantly enhance prediction of neuropsychological test performances over and above the predictive power of the apathy factor score alone.
4. Apathy factor scores will predict functional impairment (as measured by the Instrumental Activities of Daily Living scale), even when the dysphoria factor score is taken into account, but dysphoria factor scores will not significantly enhance prediction of functional impairment when the apathy factor score is taken into account.

5. If an apathy factor does not emerge, the relationship between the resulting factors and performance on neuropsychological and functional variables will be examined.

Methods

Participants

The original sample comprised 1,582 probable AD participants selected from the database of the Baylor College of Medicine's Alzheimer's Disease and Memory Disorders Center (ADMDC) in Houston, Texas, who received a comprehensive neuropsychological evaluation between December 1989 and December 2007. Evaluations were selected as the most recent annual evaluation when the list of subjects was generated in 2008. All subjects met The National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann, Drachman, & Folstein, 1984) criteria for a diagnosis of probable AD (McKhann et al., 1984) made in a multi-disciplinary consensus conference composed of neurologists, neuropsychologists, and nurses. A cutoff score greater than or equal to 15 on the Mini-Mental State Examination (MMSE) was utilized to ensure that the participants could adequately comprehend and answer items on the self-report GDS (Katz, 1998; McGivney, Mulvihill, & Taylor, 1994). This MMSE cut-off has been used by various authors to ensure the cognitive capabilities of their sample and the validity of the GDS (Chopra, Sullivan, Feldman, Landes & Beck, 2008; Hall & Davis, 2010). Complete GDS data was available for 569 patients with a mean age of 75.14 years (SD = 7.87) who constituted the final sample. See Table 5 for demographic and descriptive information on the final sample.

Patients included in this analysis were enrolled in the Baylor ADMDC and the database was approved by the Baylor Institutional Review Board. Patients and/or their

legally designated representative signed consent forms permitting the storage and use of their data.

Table 5. Sociodemographic description of the sample

Characteristic	Mean (SD)	Number	Percentage	Range
Age	75.14 (7.87)			39 – 93
Education	13.81 (6.09)			0 – 26
Estimated AD duration	3.46 (2.05)			0.5 – 13
Sex				
Female		389	68.37	
Male		180	31.63	
Race				
White/Caucasian		541	95.08	
Black/African American		24	4.22	
American Indian or Alaskan Native		1	0.18	
Asian		2	0.35	
Other		1	0.18	
Ethnicity				
Hispanic or Latino		15	2.64	
Not Hispanic or Latino		550	96.66	
Other		4	0.7	
AD Severity (MMSE)				15 – 30
Mild (MMSE ≥ 20)		338	59.4	
Moderate (MMSE 15 – 19)		231	40.6	
GDS Score	5.43 (4.86)			0 – 30
Normal range (GDS < 11)		493	86.6	
Depressed range (GDS ≥ 11)		76	13.4	

Measures

General Mental Status and Dementia Severity

The Mini-Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975) is a frequently-used measure to screen for cognitive impairment. The MMSE measures orientation to time and place, attention and calculation, immediate and delayed recall of three words, naming, repetition, comprehension, reading, writing, and visual construction. A subject's maximum score is 30 points.

Attention and concentration

Participants completed the Verbal Series Attention Test (VSAT; Mahurin & Cooke, 1996), which consists of forward and reverse generation of arithmetic series (e.g., counting backwards from 100 by 3s), verbal series (e.g., reciting months of the year forward and in reverse order), letter-number sequencing, and auditory vigilance for a target letter. Scores are calculated for both the time taken to complete each task and the number of errors made.

Memory functioning

The Logical Memory subtest of the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987) is designed to measure immediate, and delayed verbal memory. The subject is asked to recall two paragraph-length stories immediately and after a 30-minute delay. The Visual Reproduction subtest of the Wechsler Memory Scale-Revised is designed to measure visual memory. The subject is asked to reproduce four line drawings immediately and after a 30-minute delay.

Language functioning

The Boston Naming Test (BNT; Kaplan et al., 1983) was designed to assess confrontation naming. The test includes 60 black and white line drawings of objects that begin with commonly seen and named objects (e.g., bed) to lower-frequency vocabulary words (e.g., abacus).

Motor functioning

The Halstead-Reitan Finger Tapping Test (FTT; Reitan & Wolfson, 1993) will be utilized as a measure of simple motor speed. During the FTT, the examinee is instructed to tap as quickly as possible using the index finger of the dominant hand and then the non-

dominant hand on alternating trials. A specially adapted tapper and counter record number of taps over three 10-second trials per hand.

Executive Functioning

The FAS test (Spreen & Benton, 1977) was designed to assess phonemic fluency. It is also a measure of executive function that requires initiation, strategy, and mental flexibility. An examinee is asked to orally produce as many words as possible beginning with the letters F, A, and S. One minute is allotted per letter.

Assessment of Depression

As noted above, the GDS is a 30-item self-report questionnaire designed for use in a geriatric population. It is comprised of yes/no questions that measure symptoms of depression (with the exception of vegetative symptoms). Typically, a cut-off score of 11 indicates depression (Yesavage et al., 1983). This cut-off score has been used by other investigators conducting similar analyses (Adams, 2001; Wefel, Hoyt, & Massman, 1999). See Appendix 1 for a reproduction of the GDS items.

Assessment of Functional Impairment

Functional abilities were measured using the Physical Self-Maintenance Scale and Instrumental Activities of Daily Living Scale (PSMS and IADL; Lawton & Brody, 1969). The PSMS evaluates independence in six basic activities of daily living, including continence, ambulation, feeding, bathing, grooming, and dressing. Scores range from five to 30, with higher scores indicating greater impairment. The IADL scale evaluates eight complex daily living tasks, including using the telephone, shopping, housekeeping, cleaning, laundry, driving, and managing medications and finances. Scores range from zero to 31, with higher scores indicating more functional impairment. A subject's potential total is a sum of

points from the items which she ever performed, so as to better capture true loss of ability. Only subjects with no more than 3 "not applicable" items were included in the analysis. Subjects' IADL scores will be divided by their potential scores, ultimately yielding ratio scores to be used in analyses.

Proposed Analyses

An exploratory factor analysis (EFA) will be performed in Mplus Version 5 on the sample data using the weighted least squares extraction method. This method has been chosen over the principal components analysis method due to its ability to identify the unique variance accounted for by latent variables or constructs (e.g., apathy) that underlie the observed variables. This method and software are also particularly suited to EFA with dichotomous data. Given the expectation that factors will correlate, oblique rotation will be used. Number of factors retained will be determined by Cattell's scree plot of eigenvalues. Factors retained will have more than 3 items with loadings > .32 (Costello & Osborne, 2005).

The resulting factor structure will be used to create factor scores by summing raw scores corresponding to all items loading on a particular factor. In the event that different factors have different numbers of items loading, an average factor score will be calculated (i.e. number of endorsed items in Factor A/total number of items in Factor A). Then, multiple regression analyses will be conducted in SAS version 9.2 to determine the ability of dysphoria and apathy factor scores to predict functional ability and performance on the neuropsychological measures outlined above.

Before beginning these analyses, the data will be inspected for outliers. Using SAS 9.2, descriptive information will be generated for all neuropsychological and functional variables.

Results

Hypothesis 1

In order to investigate the presence of an apathy factor of the GDS in this sample, EFA was conducted on data from 569 complete GDSs, yielding seven eigenvalues greater than one. However, an examination of Cattell's scree plot demonstrated a clear break in the eigenvalues between factors four and five. Ultimately, four factors were retained. The final eigenvalues for the four factors were: 12.62, 2.13, 1.93, and 1.79, accounting for 42.06%, 7.09%, 6.42%, and 5.97% of the variance, respectively. Both the Comparative Fit Index and root mean square error of approximation indicated good model fit (CFI = 0.993 and rMSEA = 0.021). The EFA accounted for 61.54% of the total variance. The choice to use oblique rotation was substantiated by the moderate correlation between factors 1 and 2. See Table 6 below for all between-factor correlation values.

Table 6. Factor Correlation Matrix

	Factor 1 Apathy	Factor 2 Dysphoria	Factor 3 Social Withdrawal	Factor 4 Cognitive Impairment
Factor 1 (Apathy)	*1.000*			
Factor 2 (Dysphoria)	*.544*	*1.000*		
Factor 3 (Social Withdrawal)	*.187*	*.169*	*1.000*	
Factor 4 (Cognitive Impairment)	*.212*	*.259*	*.165*	*1.000*

EFA factors and item loadings appear in Table 7. Of the 30 items, four items showed cross-loadings on both factors 1 and 2. Based on the loading value difference and the items' face validity with other items on factor 2, all four items were retained and assigned to factor 2, the factor on which they loaded most highly. The secondary loading is shown in Table 7 in parentheses.

The first factor contained 12 items pertaining to apathy, with item loadings ranging from .382 to .843. Four of these items (Do you find life very exciting?, Do you feel full of

energy?, Is it hard for you to get started on new projects?, and Have you dropped many of your activities and interests?) are four of the six items that loaded onto the WAV factor in Adams' (2001) PCA on the GDS, which combined the Withdrawal/Apathy and Vigor factors previously described by Parmalee, Lawton and Katz (1989). The apathy factor in the current analysis also included three of the five items that loaded onto the apathy factor in Hall and Davis' (2010) PCA, namely, Do you feel full of energy?, Do you think it is wonderful to be alive now?, and Do you enjoy getting up in the morning? Of note, other items with strong loadings on this Apathy factor lacked face validity (e.g., Are you happy most of the time?). However, all 12 Apathy items can be related to one of the 3 apathy diagnostic domains developed by Robert et al. (2009). For example, GDS items 20, 21, and 27 correspond to symptoms of diminished behavioral initiation, and item 2 is related to diminished behavioral responsiveness. Item 29 may be associated with diminished cognitive initiation or responsiveness. Lastly, GDS items 1, 3, 5, 7, 9, 15, and 19 correspond most closely to symptoms of diminished emotional initiation or responsiveness. Of course, these GDS items do not entirely reflect the symptoms proposed by Robert et al. (2009), given that they were developed to assess geriatric depression, rather than as diagnostic items for apathy in AD.

The second factor in this EFA contained 13 items associated with dysphoric mood (e.g., worthlessness, crying, and feeling downhearted and blue). Item loadings ranged from .366 to .755. The third factor contained only two items, both pertaining to social withdrawal (i.e., Do you prefer to stay at home, rather than going out and doing new things? and Do you prefer to avoid social gatherings?). These two items were the remaining items loading on the WAV (Adams, 2001) and Apathy (Hall & Davis, 2010) factors mentioned above. Although this factor only contained two items, the loadings were adequate (.669 and .715,

respectively), and the interpretation was clear and potentially clinically relevant. Therefore, I chose to retain this Social Withdrawal factor. The fourth factor contained three items pertaining to cognitive impairment, with loadings that ranged from .666 to .744.

Table 7. Four Factor Structure of the GDS in a Sample Pure Probable AD Patients (N = 569)

ITEM	Apathy	Dysphoria	Social Withdrawal	Cognitive Impairment
Happy most of the time	*.843*			
In good spirits	*.799*			
Basically satisfied with life	*.795*			
Find life very exciting	*.763*			
Feel full of energy	*.627*			
Feel life is empty	*.622*			
Wonderful to be alive	*.590*			
Hopeful about the future	*.501*			
Enjoy getting up in the morning	*.500*			
Hard to start new projects	*.468*			
Dropped activities and interests	*.383*			
Easy to make decisions	*.382*			
Feel worthless the way you are now		*.755*		
Worry a lot about the past	*(.368)*	*.694*		
Often feel like crying		*.685*		
Frequently get upset		*.674*		
Feel downhearted and blue		*.673*		
Restless and fidgety		*.652*		
Feel situation is hopeless	*(.375)*	*.618*		
Worry about future		*.542*		
Most people better off		*.535*		
Often bored	*(.368)*	*.504*		
Feel helpless	*(.368)*	*.485*		
Bothered by thoughts		*.439*		
Afraid something bad will happen		*.366*		
Avoid social gatherings			*.715*	
Prefer to stay home			*.669*	
Mind as clear as it used to be				*.744*
Trouble concentrating				*.694*
Memory problems				*.666*
EIGENVALUES	12.617	2.128	1.927	1.791
% VARIANCE	42.06	7.09	6.42	5.97
CUMULATIVE VARIANCE	42.06	49.15	55.57	61.54

Table 8 shows the 30 GDS items in descending order of endorsement rates, as well as each item's factor assignment and item-to-total correlation. As the table shows, items pertaining to cognitive impairment were three of the four most frequently endorsed items,

consistent with a sample of mild and moderate AD patients. Of the 10 most frequently endorsed items, half were items that loaded on the Apathy factor. Only one of these top 10 items was a Dysphoria factor item. All 30 items have acceptable item-to-total correlations, ranging from .34 to .56 for the Apathy factor, from .34 to .62 for the Dysphoria factor, .38 to .42 for the Social Withdrawal factor, and from .43 to .44 for Cognitive Impairment.

Table 8. GDS Items with Endorsement Rates and Item-to-Total Correlations

Item/Subscale	Text Excerpt	% Endorsing	Item-to-Total r
30/Cognitive Impairment	Mind as clear as it used to be (No)	63.09	*.43*
14/Cognitive Impairment	Have more memory problems than most	44.82	*.33*
2/Apathy	Dropped many activities and interests	33.39	*.43*
26/Cognitive Impairment	Trouble concentrating	31.81	*.44*
21/Apathy	Feel full of energy (No)	30.76	*.52*
12/Social Withdrawal	Prefer to stay at home	29.35	*.38*
19/Apathy	Find life very exciting (No)	28.12	*.51*
20/Apathy	Hard to get started on new projects	27.24	*.49*
29/Apathy	Easy to make decisions (No)	23.55	*.39*
4/Dysphoria	Often get bored	21.79	*.56*
11/ Dysphoria	Often restless and fidgety	20.74	*.50*
28/Social Withdrawal	Prefer to avoid social gatherings	17.22	*.42*
13/ Dysphoria	Frequently worry about the future	15.64	*.54*
24/Dysphoria	Frequently get upset over little things	14.41	*.41*
17/Dysphoria	Feel pretty worthless	13.53	*.58*
6/Dysphoria	Bothered by thoughts	12.65	*.50*
10/Dysphoria	Often feel helpless	12.48	*.56*
3/Apathy	Feel your life is empty	11.78	*.56*
25/Dysphoria	Frequently feel like crying	11.42	*.43*
16/Dysphoria	Often feel downhearted and blue	10.90	*.62*
27/Apathy	Enjoy getting up in the morning (No)	10.19	*.39*
1/Apathy	Basically satisfied with life (No)	10.02	*.44*
5/Apathy	Hopeful about the future (No)	9.31	*.36*
8/Dysphoria	Afraid something bad will happen	7.21	*.45*
9/Apathy	Happy most of the time (No)	6.50	*.56*
22/Dysphoria	Feel your situation is hopeless	5.62	*.49*
7/Apathy	In good spirits most of the time (No)	4.75	*.48*
15/Apathy	Wonderful to be alive now (No)	3.69	*.34*
18/Dysphoria	Worry a lot about the past	3.16	*.34*

Given that nearly equal numbers of items loaded onto the Apathy and Dysphoria factors (12 and 13 items, respectively), factor scores were created as summed, raw totals of items endorsed in the depressed direction, rather than as a proportional score. The mean Apathy score in this sample was 1.99 (SD = 2.21) and the mean Dysphoria score was 1.58 (SD = 2.35). A paired *t*-test revealed that Apathy factor scores were significantly higher than Dysphoria scores [t (568) = 6.50, $p < .0001$].

The relationships between factor scores and continuous demographic variables were evaluated by calculating Spearman's rank correlation coefficients rather than Pearson's coefficients due to the non-normality of the factor score distributions. Although the relationship between Apathy and age was statistically significant, the value of the correlation was low (r = .12, p = .005). Neither education nor estimated AD duration were significantly associated with Apathy. Scores on the Dysphoria factor were significantly, but weakly, negatively correlated with years of education (r = -.09, p = .04). The values of the correlations between Dysphoria and age and AD duration were negligible and not statistically significant. Independent samples t-tests were performed to determine whether factor endorsement rates significantly differed by sex. For the Apathy factor, the mean score was 2.02 for males and 1.98 for females, t (567) = .26, p = .80. The average Dysphoria score for males was 1.71 and was 1.52 for females, t (567) = .89, p = .37.

Hypotheses 2 and 3

An inspection of the neuropsychological variables revealed few outliers as defined above. Also, these data points were not radical and appeared to be continuous with the rest of their respective distributions and so were not excluded or altered. Descriptive information for these variables is included in Table 9 below. An examination of factor score frequencies

revealed strong positive skewness in the distributions of both factors of interest, indicating that 30.58% of patients endorsed 0 Apathy items and 47.98% of subjects endorsed 0 Dysphoria items. Based on these results, it was determined that regression analyses would not be appropriate.

Table 9. Descriptive Information for Neuropsychological and Functional Variables

Variable	N	Mean (SD)	Range
Logical Memory I	550	6.75 (5.54)	0 – 32
Logical Memory II	543	1.44 (3.32)	0 – 29
Visual Reproduction I	544	13.57 (7.60)	0 – 40
Visual Reproduction II	540	1.94 (4.59)	0 – 36
BNT	549	38.17 (13.61)	0 – 60
FAS	524	23.49 (11.96)	0 – 65
VSAT time	549	216.25 (96.64)	53 – 452
FTT dominant	515	37.84 (11.20)	8.67 – 64.33
FTT non-dominant	514	35.17 (9.74)	7.33 – 61.7
PSMS	478	8.42 (3.34)	6 – 23
IADL ratio	489	.90 (.18)	.25 – 1

Instead, factor scores were used to create two levels of Dysphoria and Apathy. The first level included only those subjects who had a factor score of 0 (174 had a score of 0 for Apathy and 273 subjects had a score of 0 for Dysphoria). The second level included subjects who had Apathy scores greater than or equal to 3 or Dysphoria scores greater than or equal to 2, denoting the presence of Apathy or Dysphoria. The lower cut-off for Dysphoria was adopted due to the patients' lower scores on Dysphoria than Apathy, and thus to ensure adequate sample sizes in all four of the Apathy/Dysphoria subgroups (cells). Based on this cut-off, 168 subjects (29.5%) met criteria for the Apathy group and 193 (33.9%) met criteria for the Dysphoria group. Of the original 569 subjects, 287 met criteria for one of the four subgroups formed. Group 1 included 120 subjects with neither Dysphoria nor Apathy, group 2 included 30 subjects with Dysphoria only, group 3 included 43 subjects with Apathy only,

and group 4 included 94 subjects with both Dysphoria and Apathy. Cell assignment was not associated with group differences in age or education. The two groups with 3 or more symptoms of apathy were associated with shorter estimated AD duration (mean of Apathy groups = 3.09, mean of No Apathy groups = 3.77, $p = .023$), but this relationship was associated with a small effect size ($r^2 = .018$). As expected, the mean GDS scores in each of the cells differed. The relationship between groups and GDS scores was associated with a significant Apathy x Dysphoria interaction effect ($p < .0001$). Post-hoc analyses revealed that, even after Bonferroni correction, the mean GDS total score for the Apathy only group was significantly higher than that of the group with neither Apathy nor Dysphoria and lower than the group with both Apathy and Dysphoria (both $p < .0001$). The Dysphoria only group showed the same relationships (both $p < .0001$). Interestingly, there was no significant difference between the mean GDS scores of the Dysphoria only and Apathy only groups ($p < .07$). See Table 10 for additional details.

Table 10. Means and Standard Deviations of GDS Total Scores by Group

	Group 1 Neither Apathy nor Dysphoria	**Group 2 Dysphoria Only**	**Group 3 Apathy Only**	**Group 4 Apathy and Dysphoria**
GDS Total	0.99 (1.12)	4.43 (1.65)	5.72 (1.61)	13.72 (4.78)

These 4 groups were entered into 2x2 ANOVAs to determine any differences in performance on the neuropsychological variables. Of note, not all of these patients had data from all neuropsychological measures mentioned above. Given the unequal cell sizes, analyses utilizing Type III sums of squares were conducted. Means and standard deviations for all variables in each of the four subgroups are shown in Table 11.

Table 11. Means and Standard Deviations of All Dependent Variables by Group

Variable	Group 1 Neither Apathy nor Dysphoria	Group 2 Dysphoria Only	Group 3 Apathy Only	Group 4 Apathy and Dysphoria
Logical Memory I	6.64 (5.35)	7.78 (6.11)	4.76 (4.21)	6.71 (5.82)
Logical Memory II	0.08 (2.36)	1.03 (2.53)	1.29 (3.14)	1.92 (4.27)
Visual Reproduction I	13.59 (7.41)	13.34 (7.38)	14.18 (7.01)	12.18 (7.59)
Visual Reproduction II	1.53 (3.18)	0.72 (1.41)	1.45 (3.17)	2.27 (5.89)
BNT	39.72 (13.29)	37.50 (12.68)	39.77 (13.36)	35.84 (13.89)
FAS	25.06 (11.48)	24.97 (13.02)	22.46 (10.11)	21.67 (12.18)
VSAT time	206.43 (73.95)	211.63 (81.39)	191.30 (61.73)	217.58 (81.63)
FTT dominant	39.98 (11.10)	38.58 (11.60)	33.49 (10.47)	36.25 (12.14)
FTT non-dominant	36.69 (9.32)	36.07 (9.29)	31.28 (9.84)	34.34 (10.80)
PSMS	8.22 (2.98)	8.00 (3.45)	9.06 (3.46)	9.21 (3.76)
IADL ratio	0.85 (0.22)	0.98 (0.06)	0.90 (0.19)	0.90 (0.19)

Results of the ANOVAs indicated that the Apathy x Dysphoria interaction was not significant for any of the neuropsychological variables (see Table 11). Apathy was associated with significantly lower scores on the Logical Memory Immediate Recall subtest and fewer taps on the Finger Tapping Test with both dominant and non-dominant hands. On the Logical Memory Immediate Recall subtest, the group with at least 3 symptoms of Apathy had a mean score of 6.26, while the group without any symptoms had a mean score of 7.04 (p = .047). On the Finger Tapping Test, the subjects who endorsed at least 3 symptoms of Apathy completed an average of 35.35 taps with their dominant hand and 33.37 with their non-dominant hands, as compared to those without apathy who completed 39.70 and 36.56 taps, respectively (p = .007, p = .013). Although statistically significant, the relationships between apathy and immediate verbal memory and motor speed with dominant and non-dominant hands were associated with small effect sizes (r^2 = .014, .028, and .024, respectively). A significant main effect of Dysphoria was not present for any neuropsychological variable. A detailed description of these findings can be found in Table 12.

Hypothesis 4

In order the investigate the relationship between scores on the Apathy and Dysphoria factors and functional impairments, an Instrumental Activities of Daily Living ratio score was entered as a dependent variable in the 2x2 ANOVA described above. An examination of the frequencies of IADL potential totals revealed a substantial number of subjects who had more than 3 non-applicable items on this measure, meaning that they reported having never performed the task. After adhering to the procedures outlined above, only 150 subjects' IADL ratio scores were eligible for analysis. Apathy was significantly associated with greater functional impairment (p = .046), as measured by PSMS (see Tables 11 and 12). Of note, this relationship also had a small effect size (r^2 = .016). Neither apathy nor dysphoria was associated with impairment in more complex activities of daily living (IADL ratio scores).

Table 12. p-values for Main and Interaction effects for Neuropsychological Variables

Variable	N	Apathy (main effect)	Dysphoria (main effect)	Interaction (Apathy x Dysphoria)
BNT	276	*0.67*	*0.10*	*0.65*
Logical Memory I	279	*< 0.05****	*0.06*	*0.60*
Logical Memory II	275	*0.14*	*0.37*	*0.63*
Visual Reproduction I	275	*0.45*	*0.55*	*0.19*
Visual Reproduction II	272	*0.22*	*0.99*	*0.17*
FAS	264	*0.08*	*0.79*	*0.84*
VSAT	279	*0.66*	*0.14*	*0.32*
FTT dominant	261	*< 0.01****	*0.67*	*0.20*
FTT non-dominant	261	*< 0.01****	*0.39*	*0.20*
PSMS	245	*< 0.05****	*0.95*	*0.71*
IADL	150	*0.78*	*0.08*	*0.08*

* Denotes statistically significant *p*-value

Discussion

Hypothesis 1 was essentially supported by the data. A factor largely representative of apathy did emerge and accounted for 42% of the total variance. Although previous factor analytic studies of the GDS have yielded a component related to apathy, ours is the first in which apathy emerged as the first factor, accounting for the most variance. This apathy factor

also had 12 items load on it, at least twice as many as other studies have found. The items loading on this Apathy factor included four of the six items that loaded onto the Withdrawal/Apathy and Vigor component in Adams' (2001) PCA, four of the six items that loaded onto the Apathy component in Hall and Davis' (2010) PCA, two of the four items that loaded onto the Withdrawal/Avoidance component in Salamero and Marcos' (1992) PCA, and two of the four items that loaded onto the Withdrawal/Apathy component in Parmalee et al.'s (1989) PCA. In all four cases, the remaining two items were those that constitute the Social Withdrawal items in this study. As these studies included either a cognitively intact or cognitively mixed sample, this finding suggests that certain symptoms of apathy are consistent in the geriatric population, regardless of cognitive status.

On the other hand, the Apathy factor in the current study also included items that loaded onto Abraham et al.'s (1991) Life Dissatisfaction component ad those that loaded onto Bentz and Hall's (2008) Hopelessness component. Nevertheless, one can make the argument that these items (e.g., Are you basically satisfied with your life?, Do you find life very exciting?, and Do you enjoy getting up in the morning?) are consistent with diminished concomitants of goal-directed behavior (diminished emotional initiation or responsiveness), one of the three apathy symptom diagnostic domains as defined by Starkstein et al. (2001) and Robert et al. (2009). Taken together, these findings may mean that the clinical presentation of apathy is distinct in AD from that in other cognitive disorders or in normal aging. Based on the items that loaded onto the present Apathy factor, it appears that apathy in AD may be characterized by a sense of life dissatisfaction resulting from diminished emotional responsivity, as well as an overall sense of diminished motivation.

As in previous studies, the results of the current factor analysis yielded factors reflecting dysphoria (Abraham et al., 1992; Adams, 2001; Hall & Davis, 2010; Parmalee et al., 1989; Salamero & Marcos, 1992; and Sheihk et al., 1991), social withdrawal (Abraham et al., 1992; Bentz & Hall, 2008; Parmalee et al., 1989; Salamero & Marcos, 1992; and Sheihk et al., 1991), and cognitive impairment (Abraham et al., 1992; Adams, 2001; Hall & Davis, 2010; Parmalee et al., 1989; and Salamero & Marcos, 1992). As noted above, several previous studies yielded factors that incorporated symptoms of both apathy and social withdrawal. Although it is reasonable to assume that apathy would be associated with social isolation, the latter constituted a distinct factor in this case. In the case of AD, patients may withdraw socially as a result of embarrassment about cognitive decline, increased confusion in unfamiliar environments, and/or impaired activities of daily living (e.g., driving).

An analysis of item frequencies revealed that items loading onto Cognitive Impairment and Apathy were among those most frequently endorsed in this sample. A comparison of item frequencies with that of Adams' (2001) PCA showed nine of the same most frequently endorsed items. The most obvious difference between the two studies was the more frequent endorsement of Cognitive Impairment items in the present study. In fact, the most commonly endorsed item was "Do you feel you have more memory problems than most?," consistent with this sample of AD patients. Ultimately, this EFA on the GDS in a large sample of subjects with pure Probable AD yielded factors that map well onto commonly recognized correlates of AD: apathy, dysphoria, social withdrawal, and cognitive impairment. Of note, the factor structure generated in the present study accounted for a greater percentage of total variance in the GDS than was explained by any previous study.

An examination of the relationship between factors and demographic variables revealed that patients with apathy were significantly older than those patients without apathy, a finding also reported by Starkstein et al. (2006b). The relationship between apathy and gender was not significant, consistent with some previous literature (Landes et al., 2001; Landes et al., 2005), but in contrast to other investigators who found apathy to be related to male gender (Ott et al., 1996). Dysphoria was associated with fewer years of education.

Hypotheses 2 and 3 required the creation of summed factor scores. A comparison of the Apathy and Dysphoria factors showed that the mean Apathy score was significantly higher than the mean Dysphoria score in the sample. The finding that apathy is more frequently experienced in AD, as compared to depression, is consistent with results from previous studies (Landes et al., 2005). As expected, the Apathy and Dysphoria factors were moderately correlated; however, relative lack of cross-loading items bolsters the evidence for these two factors and syndromes as distinct in AD.

Approximately one third of the sample did not endorse any Apathy items and approximately one half did not endorse a Dysphoria item. This finding was not particularly surprising in light of the sample's mean GDS score of 5.43. However, this low prevalence of depressive symptomatology was surprising, based on the higher prevalence rates reported in the literature. This finding may be the result of restricting subjects to those with an MMSE score of at least 15. If, as some previous studies have suggested, the incidence and severity of depression and apathy increase with AD severity, then this inclusion criteria may have unduly limited the range of GDS scores in this sample. In addition, analyzing data from patients' most recent evaluations involved the inclusion of patients who had been prescribed antidementia and antidepressant medications for varying lengths of time. Both the presence

and duration of these medications could have impacted the frequency of depressive and apathetic symptoms in our sample. A final potential explanation for the low frequency of depressive symptoms is patient's involvement with the Baylor College of Medicine's Alzheimer's Disease and Memory Disorders Center. The type of specialized assessment and treatment provided, access to resources, and ongoing yearly evaluations may actually reduce symptoms of depression.

As noted above, a strong positive skewness in the distributions of the Apathy and Dysphoria factors precluded the implementation of the proposed regression analyses. Instead, using the cut-off scores detailed above, four groups were formed based on their Apathy and Dysphoria scores. The proportion of subjects meeting criteria for each of these groups largely mirrors the findings of Starkstein et al. (2001). In both cases, approximately 42% of subjects were classified as having neither apathy nor depression. The number of subjects who met criteria for apathy only was also similar (15% of subjects in this study, compared to 13% in Starkstein et al., 2001). This is notable, given that these other authors used specific diagnostic criteria for apathy in AD adapted from Marin (1991). This finding is evidence for the criterion validity of the Apathy factor and implies responses to these 12 GDS items may be able to accurately identify the presence of apathy in AD. Conversely, the number of subjects who met criteria for dysphoria (10%) in the present study was fewer than that found by Starkstein et al. (2001) with more stringent DSM-IV criteria for Major Depressive Disorder or Dysthymia (22%). Again, the restricted range of AD severity in this sample may at least partially explain this discrepancy. Of note, a greater percentage of our sample endorsed symptoms of *both* apathy and dysphoria (33%, compared to 24% in Starkstein et al., 2001),

which suggests that a greater frequency of apathy in our sample may have also contributed to this difference.

Analyses with 2x2 ANOVAs demonstrated that the presence of three or more symptoms of apathy was associated with greater impairments in verbal memory and motor speed. These findings are consistent with those of Kuzis, et al. (1999), Sperry et al. (2001), and Starkstein, et al. (2001). As noted above, these statistically significant relationships were associated with small effect sizes. Unlike previous studies, results from the present analysis did not yield a significant relationship between apathy and performance on measures of verbal fluency or confrontation naming. The restriction of disease severity to patients with mild-to-moderate AD may have diminished the relationships between symptoms of apathy and cognitive variables. As in Kuzis et al. (1999) and Sperry et al. (2001), depression was not significantly associated with performance on any neuropsychological or functional measure. Overall, these findings partially supported hypotheses two and three.

Hypothesis 4 predicted that subjects with increased scores on the Apathy factor would show greater functional impairment. This hypothesis was partially supported by the data. Apathy was associated with greater functional impairment in basic activities of daily living (e.g., bathing, dressing, and eating), as measured by PSMS. Neither apathy nor dysphoria was associated with greater functional impairment in complex activities of daily living. As discussed earlier, this sample had a high number of patients with low potential IADL totals, meaning that subjects reportedly never performed these activities and so could not report diminished abilities. This IADL variable can be problematic in that it requires knowledge and evaluation of what a person has habitually done in their lifetime. As explained above, patients who had more than three activities that they never performed were eliminated from

the analyses, reducing the sample size and diminishing the strength of the relationship between factor scores and this variable.

This study has several potential limitations that warrant attention. Given the sample's relatively high level of education, middle-to-high socioeconomic status, and racial and ethnic homogeneity (predominantly Caucasian), the results may not be generalizable to all patients with AD. Moreover, these patients are somewhat unique in that they sought out the specialized assessment and care provided by Baylor College of Medicine Alzheimer's Disease and Memory Disorder Center.

Another issue to consider is that nine of the ten reverse-scored items on the GDS loaded on the Apathy factor, and none of the reverse-scored items loaded on the Dysphoria factor. As a result, patients with a negative response bias (a tendency to respond "no" to questions when unsure) would tend to get higher Apathy than Dysphoria scores and patients with a positive response bias would tend to get higher Dysphoria scores. However, considering the low mean Apathy and Dysphoria scores, it appears that this potentially confounding factor did not play a substantial role in the current study.

Based on the above findings, scoring the 12 items that loaded onto the Apathy factor may have clinical utility as a screening measure for symptoms of apathy in AD. Although our results did not support the hypothesis that symptoms of apathy would uniquely contribute to cognitive impairment in multiple domains, other investigators have found powerful relationships between apathy and cognitive impairment, functional impairment, decreased quality of life, and increased caregiver burden. For those clinical practices that routinely use the GDS in their battery to assess and diagnose patients with AD, the GDS may also be

helpful in identifying patients at risk for clinically significant apathy. Early identification will allow for early education and intervention, hopefully reducing patient and caregiver burden.

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Appendix A. Items of the Geriatric Depression Scale

1. Are you basically satisfied with your life?
2. Have you dropped many of your activities and interests?
3. Do you feel that your life is empty?
4. Do you often get bored?
5. Are you hopeful about the future?
6. Are you bothered by thoughts you can't get out of your head?
7. Are you in good spirits most of the time?
8. Are you afraid that something bad is going to happen to you?
9. Do you feel happy most of the time?
10. Do you often feel helpless?
11. Do you often get restless and fidgety?
12. Do you prefer to stay at home, rather than going out and doing new things?
13. Do you frequently worry about the future?
14. Do you feel you have more problems with memory than most?
15. Do you think it is wonderful to be alive now?
16. Do you often feel downhearted and blue?
17. Do you feel pretty worthless the way you are now?
18. Do you worry a lot about the past?
19. Do you find life very exciting?
20. Is it hard for you to get started on new projects?
21. Do you feel full of energy?
22. Do you feel that your situation is hopeless?
23. Do you think that most people are better off than you are?
24. Do you frequently get upset over little things?
25. Do you frequently feel like crying?
26. Do you have trouble concentrating?
27. Do you enjoy getting up in the morning?
28. Do you prefer to avoid social gatherings?
29. Is it easy for you to make decisions?
30. Is your mind as clear as it used to be?