APATHY, GENETICS, AND FUNCTIONAL STATUS IN PERSONS WITH ALZHEIMER DISEASE

By

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ABSTRACT

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Background/Significance: Alzheimer Disease (AD) is an irreversible dementia that progressively destroys cognitive and daily functioning. About 5.4 million Americans currently suffer from AD, with estimated prevalence to reach 16 million by 2050 (Alzheimer's Association, 2012). AD is often regarded with fear, as most affected individuals eventually fail to recognize loved ones, lose the ability to care for themselves, and may display negative neuropsychiatric behaviors, such as apathy. Apathy is a disorder of motivation with deficits in behavioral, emotional, and/or cognitive domains and is conceptualized as a need-driven behavior, based on the Need-Driven Dementia-Compromised Behavior Model (Algase et al., 1996). **Problem:** Despite the high prevalence and negative sequela associated with apathy, little is known about characteristics of persons with AD, including biologic factors that contribute to the presence and severity of apathy. **Purpose:** The purpose of this study was to examine the extent to which individual characteristics and social environment factors predict apathy in persons with AD and the extent to which apathy influences function. **Specific Aims:** 1) Examine the extent to which individual characteristics (demographics and cognitive status) and social environment factors predict the severity of apathy in persons with AD, after adjusting for AD severity and *Apolipoprotein E-4 (APOE4)* status, 2) Examine the extent to which variations in the *Oxytocin Receptor (OXTR)* gene are associated with apathy in persons with AD, and 3) Examine the extent to which severity of apathy influences functional status in persons with AD, after adjusting for AD severity. **Methods:** This cross-sectional descriptive study of 66 persons

with moderate dementia was part of a parent study of gene-environment interactions in the symptoms of AD, in which persons with a diagnosis of possible or probable AD were recruited from the community and long-term care facilities. **Instrumentation:** Measures of cognition (Severe Impairment Battery [SIB]), apathy (Neuropsychiatric Inventory-Nursing Home, Apathy subscale [NPI-Apathy] and Apathy Inventory [IA]), function (Functional Assessment Staging Test [FAST] and Functional Abilities Checklist [FAC]), as well as deoxyribonucleic acid (DNA) for subsequent genotyping, were available to address these aims. **Results:** The majority of study participants were female, with a mean age of 85 years (SD=7.35). The prevalence of apathy ranged from 53-72%, depending on the measure of apathy. ***Aim 1:*** Multiple linear regression produced a model that explained 24.5% of the variance in apathy severity (F=2.370, p=.046). Background factor variables [main demographic variables (age, gender) and cognition (SIB total score)], function (FAST total score), and number of *APOE4* alleles served as the most significant and parsimonious predictors of apathy (NPI-Apathy). ***Aim 2:*** A DNA variant within the *OXTR* gene (rs53576) significantly predicted 19.4% of the variance in apathy severity (NPI-Apathy) (F=3.379, p=.027), while controlling for cognitive status and number of *APOE4* alleles. The AA genotype was associated with more severe apathy. ***Aim 3:*** Both presence of apathy and apathy severity predicted overall function as measured by FAST score, controlling for cognitive status. **Implications:** This study is an important step in explicating the relationship between individual characteristics, such as genetics, apathy, and functional status in persons with AD. The relationship between apathy and *OXTR* genotype status must be further explored, along with the predictive ability of *OXTR* genotype status on apathy severity. This contribution will help to provide a foundation for the development of rigorous and tailored interventions to increase meaningful engagement, reduce apathy and increase QOL in this vulnerable population.

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This work is dedicated to my parents for their encouragement and support throughout my education and to my dearly loved husband, Don.

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TABLE OF CONTENTS

LIST OF TABLES ……..……xiv

LIST OF FIGURES ……xvii

CHAPTER 1: INTRODUCTION……..……..1
Background and Significance……..……1
Alzheimer Disease (AD)……..……..…….1
Behavioral Symptoms in Alzheimer Disease (AD)……...……..2
Apathy…….……4
Apathy in Persons with Alzheimer Disease (AD)…….…..……4
Genetic Risk Factors for Apathy……..7
Problem Statement……...8
Purpose of the Study……....8
Specific Aims……...…9
Aim 1……..….9
Hypothesis……....9
Aim 2……...9
Hypothesis……...9
Aim 3……10
Hypothesis…….….10
Study Design and Innovation……10
Summary……10

CHAPTER 2: THEORETICAL FRAMEWORK…….……12
Apathy……12
Apathy in the Context of Emotion and Meaning……...16
Need-Driven Dementia-Compromised Behavior (NDB) Model……...20
Historical Development……20
Description of the Need-Driven Dementia-Compromised Behavior (NDB) Model……20
Evaluation of the Need-Driven Dementia-Compromised Behavior (NDB) Model……22
Analysis…….……22
Theory scope and context……..……22
Theory content……..……23
Evaluation…….……24
Significance……..……..24
Internal consistency……..……24
Parsimony…….……25
Testability…….……25
Empirical adequacy……...……26
Pragmatic adequacy……...……26
Adapted Model for Dissertation Study……..……..…..27

CHAPTER 3: REVIEW OF THE LITERATURE……30
Alzheimer Disease (AD)……30
History of Alzheimer Disease (AD)……30
Alzheimer Disease (AD) Phenotype……30
Epidemiology of Alzheimer Disease (AD)……31
Complex Etiology of Alzheimer Disease (AD)……32
Negative Sequela of Alzheimer Disease (AD)……35
Symptoms in Alzheimer Disease (AD)……35
Cognitive decline……35
Behavioral symptoms……36
Apathy in Alzheimer Disease (AD)……38
Operational Definition of Apathy……38
Factors Associated with the Presence and Severity of Apathy……40
Background Factors……40
Demographic characteristics……40
Genetics……41
Cognitive abilities……43
Proximal Factors……44
Social environment……44
Function……45
Nonpharmacologic Interventions for Reducing Apathy in Persons with Dementia……49

CHAPTER 4: METHODS/APPROACH……52
Study Design……52
Sample and Setting……52
Inclusion criteria……53
Exclusion criteria……53
Instrumentation: Background Factors……53
Demographic Characteristics……53
Genotype/Genetic Measurement……53
Cognitive Abilities……54
Severe Impairment Battery (SIB)……54
Instrumentation: Proximal Factors……55
Social Environment……55
Categorical variable……55
Ambiance Scale (AS)……56
Instrumentation: Need Driven Behaviors……57
Apathy……57
Neuropsychiatric Inventory-Nursing Home (NPI-NH)……57
Apathy Inventory (IA)……58
Instrumentation: Function……61
Functional Abilities Checklist (FAC)……61
Functional Assessment Staging for Alzheimer Disease (FAST)……61
Procedures……62
Recruitment Procedures……62

Data Collection Procedures……..…….62
Sample processing and genotyping procedures…….64
SNP identification and testing…….……..66
Data Analysis…….66
General Data Analysis Strategies…….……..66
Data Analysis Strategies by Specific Aims……..……67
Aim 1. Examine the extent to which individual characteristics (demographics and cognitive status) and social environment factors predict the severity of apathy in persons with AD, after adjusting for AD severity (based on FAST scale score) and *APOE* status……..…….67
Aim 2. Examine the extent to which variations in the *Oxytocin Receptor (OXTR)* gene are associated with apathy in persons with AD……..…68
Aim 3. Examine the extent to which severity of apathy influences functional status in persons with AD, after adjusting for AD severity……...……68

CHAPTER 5: RESULTS……...……70
Sample and Key Variable Description……..……..……...70
Background Factors…….……..71
Demographic characteristics…….……..…71
Genotype/genetic measurement…….72
Apolipoprotein E (APOE)…….……72
Oxytocin Receptor (OXTR) gene…….....…74
Relationships among *APOE4* and *OXTR* genotypes……..74
Cognitive abilities…….…….74
Proximal Factors……77
Social environment……...…….77
Place of residence……..……77
Ambiance Scale (AS)……..……..78
Relationships among measures of social environment…….….79
Need Driven Behavior (NDB) (Outcome Variable)……..…80
Behavioral symptoms…….80
Apathy……..……..81
Presence of apathy…….……81
Presence of apathy (NPI-Apathy)…….…….81
Presence of apathy (IA)……...……..82
Severity of apathy……..……84
Severity of apathy (NPI-Apathy)……..…….84
Severity of apathy (IA total score)…….86
Severity of apathy (IA subscales)……..87
Relationships among measures of apathy……..……88
Function……...……..92
Functional Assessment Stating (FAST) tool……..92
FAST score and presence of apathy……..…….93

FAST score and severity of apathy……..…..93
Functional Abilities Checklist (FAC)……..…….95
Function (FAC Score) and presence of apathy (NPI-Apathy)…….…..….97
Function (FAC Score) and severity of apathy (NPI-Apathy)……...….99
Function (FAC Score) and severity of apathy (IA)……..……..99
Relationships among measures of function…….100
Results by Specific Aim……...101
Aim 1. Examine the extent to which individual characteristics (demographics and cognitive status) and social environment factors predict the severity of apathy in persons with AD, after adjusting for AD severity (based on FAST scale score) and *APOE4* status……..……101
Individual characteristic predictors of presence of apathy……..……101
Individual characteristic predictors of severity of apathy……..…..101
Modeling predictors of presence of apathy……..102
Modeling predictors of severity of apathy……...……103
Aim 2. Examine the extent to which variations in the *Oxytocin Receptor (OXTR)* gene are associate with apathy in persons with AD……...….107
Relationships between *OXTR* SNPs and presence of apathy……...……108
Relationships between *OXTR* SNPs and presence of apathy (NPI-Apathy)……..108
Relationships between *OXTR* SNPs and presence of apathy (IA)……..…….……..108
Modeling relationships between *OXTR* SNPs and presence of apathy…….…….109
Relationships between *OXTR* SNPs and severity of apathy (NPI-Apathy)……..……109
Relationships between *OXTR* SNPs and severity of apathy (IA)……..……...……109
Modeling relationships between *OXTR* SNPs and severity of apathy (NPI-Apathy)……...….112
Aim 3. Examine the extent to which severity of apathy influences functional status in persons with AD, after adjusting for AD severity…….114
Relationships between function and presence of apathy……...……..114
Relationships between function and severity of apathy……...……115
Presence of apathy and functional status…….……115
Modeling relationships between presence of apathy and functional status (FAST score)……..……..115
Modeling relationships among presence of apathy and functional status (FAC subscales)……..……..116

Severity of apathy and functional status……117
Severity of apathy and functional status (FAST score)……117
Severity of apathy and functional status (FAC subscales)……118
Results Summary……120

CHAPTER 6: DISCUSSION……122
Key Findings Related to Sample Characteristics……122
Demographic Characteristics……122
Genotype/Genetic Measurement……123
Apolipoprotein E (APOE)……123
Oxytocin Receptor (OXTR) gene……125
Cognitive Abilities……125
Social Environment……126
Behavioral Symptoms……126
Apathy……127
Predictors of the Presence of Apathy……130
Individual Associations……130
Modeling the Presence of Apathy……131
Predictors of the Severity of Apathy……131
Individual Associations……131
Modeling the Severity of Apathy……132
Oxytocin Receptor (OXTR) gene as a Predictor of the Presence and Severity of Apathy……132
Relationships among *Oxytocin Receptor (OXTR)* gene SNPS and Presence of Apathy……133
Relationships among *Oxytocin Receptor (OXTR)* gene SNPS and Severity of Apathy……133
Relationships among Apathy and Functional Outcomes……136
Relationships between the Presence of Apathy and Function……136
Relationships between Severity of Apathy and Function……137
Limitations……139
Implications for Future Nursing Research……142
Implications for Policy and Nursing Practice……143
Conclusion……144

APPENDICES……146
MEASURES……147
Demographic Questionnaire……148
Severe Impairment Battery (SIB)……151
Ambiance Scale (AS)……152
Neuropsychiatric Inventory-Nursing Home (NPI-NH)……153
Apathy Inventory (IA)……178
Functional Abilities Checklist (FAC)……180
Functional Assessment Staging Tool (FAST)……182
PROTECTION OF HUMAN SUBJECTS……183

REFERENCES……...…….187

LIST OF TABLES

Table 1. Comparison of the Constructs and Psychometrics of the IA and NPI-NH……...….60

Table 2. Data Collection Summary……...…….....64

Table 3. Specific Aim 2 SNP Selection…….……66

Table 4. Sample Characteristics: Demographic Variables……71

Table 5. Age of Symptom Onset by Number of *APOE4* alleles……72

Table 6. Allele and Genotype Frequencies……73

Table 7. *APOE4* and *OXTR* Genotype Correlations……..75

Table 8. Descriptive Results Related to Cognition……76

Table 9. Cognition (as Measured by SIB total score) by Gender……..…76

Table 10. Descriptive Results Related to Social Environment - Place of Residence……...78

Table 11. Mean Differences in Demographic and Cognitive Characteristics of Total Sample by Place of Residence…….…….78

Table 12. Behavioral Symptom Frequencies (NPI-NH)……80

Table 13. Apathy Prevalence and Severity according to the NPI and IA Instruments……..……..……..……..……..…….82

Table 14. Mean Differences in Demographic and Cognitive Characteristics by Presence of Apathy (NPI-Apathy)……82

Table 15. Mean Differences in Demographic and Cognitive Characteristics by Presence of Apathy (IA)……...83

Table 16. Apathy Prevalence and Severity (as Measured by NPI-Apathy) by Gender……...84

Table 17. Relationship between Demographic Characteristics, Cognitive Characteristics, and Apathy Severity (as Measured by NPI-Apathy) – Correlations……..…….85

Table 18. Apathy Disruption Scores for Persons Exhibiting Apathy (NPI)……..86

Table 19. Apathy Prevalence and Severity (as Measured by IA Total Score) by Gender……...86

Table 20. Relationships among Demographic Characteristics, Cognitive Characteristics, and Apathy Severity (as Measured by IA Total Score)……...…88

Table 21. Presence of Apathy (NPI-Apathy) and Apathy Severity (IA Subscales)……..90

Table 22. Relationships Among Measures of Apathy……...91

Table 23. Comparison of Functional Status by Gender using FAST scale……...92

Table 24. Relationships among Demographic Characteristics, Cognitive Characteristics, and Function (as Measured by FAST score and FAC Subscales)…...94

Table 25. Functional Characteristics of the Sample……..……..……..……96

Table 26. Mean Function (FAC Subscales) by Gender……..……..……..……...96

Table 27. Mean Function (FAC Subscales) by Presence of Apathy (NPI-Apathy)……..98

Table 28. Mean Function (FAC Subscales) by Presence of Apathy (IA) ……..…98

Table 29. Relationships Among Measures of Function…….……..……..……..……100

Table 30. Gender, Age, and Cognition (SIB total score) as Predictors of Apathy Severity (NPI-Apathy)……..…..105

Table 31. Comprehensive Predictors of Apathy Severity (NPI-Apathy)……..…..……106

Table 32. Apathy Severity by *OXTR1* (rs237885) Genotype……..……..……..…110

Table 33. Apathy Severity by *OXTR2* (rs53576) Genotype……..……..……110

Table 34. Apathy Severity by *OXTR3* (rs237885) Genotype……..……..……...111

Table 35. Apathy Severity by *OXTR4* (rs6770632) Genotype……..……..……111

Table 36. Apathy Severity by *OXTR5* (rs2268491) Genotype……..……..……112

Table 37. Correlations between Apathy Severity and *OXTR* Genotype in Persons with AD……..……..……..……..……..……..……...112

Table 38. *OXTR2 (*rs53576), Cognition (SIB total score), and *APOE4* as Predictors of Apathy Severity (NPI-Apathy)……..…..113

Table 39. *OXTR3* (rs237885), Cognition (SIB total score) and *APOE4* as Predictors of Apathy Severity (NPI-Apathy)……...113

Table 40. Presence of Apathy (NPI-Apathy*)* and Cognition (SIB total score) as Predictors of Function (FAST score)……..116

Table 41. Presence of Apathy (NPI-Apathy) and Cognition (SIB total score) as Predictors of Function (FAC Self Care subscale)……117

Table 42. Presence of Apathy (NPI-Apathy) and Cognition (SIB total score) as Predictors of Function (FAC Cognitive Status subscale)……117

Table 43. Severity of Apathy (NPI-Apathy) and Cognition (SIB total score) as Predictors of Function (FAST score)…….....118

Table 44. Severity of Apathy (NPI-Apathy) and Cognition (SIB total score) as Predictors of Function (FAC Self Care subscale)……119

Table 45. Severity of Apathy (NPI-Apathy) and Cognition (SIB total score) as Predictors of Function (FAC Cognitive Status subscale)……...……119

Table 46. Severity of Apathy (NPI-Apathy) and Cognition (SIB total score) as Predictors of Function (FAC Agitated Behaviors subscale)……...120

LIST OF FIGURES

Figure 1. The Need-Driven Dementia-Compromised Behavior Model (Algase et al., 1996)……21

Figure 2. Adapted Model for use in Dissertation Study: Apathy, Genetics, and Functional Status in Persons with Alzheimer Disease……29

Figure 3. Apathy as Measured by Apathy Inventory Total Score and NPI-Apathy Frequency x Severity Score (n=21)……...89

CHAPTER 1: INTRODUCTION

Background and Significance

Alzheimer Disease (AD). Alzheimer Disease (AD) is an irreversible dementia that progressively destroys cognitive and daily functioning and is frequently accompanied by challenging behavioral symptoms. Substantial variability occurs in the severity of these behavioral and cognitive symptoms in persons with AD throughout the disease. AD is often regarded with fear, as most affected individuals eventually fail to recognize loved ones, lose the ability to care for themselves, and may display negative neuropsychiatric behaviors.

About 5.4 million Americans currently suffer from AD (Alzheimer's Association, 2012). By 2050, the Alzheimer's Association (2012) estimates that the number of individuals with AD may reach 16 million. AD is the sixth-leading cause of death in the United States, with 15 million Americans providing unpaid care to individuals with AD and other dementias (Alzheimer's Association, 2012). Many times, individuals with AD are placed in assisted living facilities or traditional nursing homes in order to ensure their safety and proper care due to the progressive nature of the disease. For the year 2012, it is estimated that the direct costs of caring for persons with AD to American society will total over $200 billion, including $140 billion in costs to Medicare and Medicaid (Alzheimer's Association, 2012).

Dementia is a general term describing decline in mental ability to the extent that it interferes with daily life (Alzheimer's Association, 2012). AD is a type of dementia, and classifications for AD include mild, moderate, and severe stages. While there are both early-onset and late-onset forms of the disease, AD most often manifests after age 60, impacting nearly every facet of daily life (National Institute on Aging, 2013). The average duration of AD is eight to ten years, with a range from one year to twenty-five years (Bird, 2010). AD is characterized,

initially, by subtle and often poorly recognized memory failure. It becomes increasingly severe and eventually incapacitating (Aderinwale, Ernst, & Mousa, 2010; Bird, 2010). Common clinical features of AD include confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations (Bird, 2010). The disease progressively destroys neurons in the cortex and limbic structures of the brain, impacting areas responsible for learning, memory, behavior, emotion, and reasoning (Aderinwale et al., 2010).

There is currently no cure for this devastating disease (National Institute on Aging, 2013). Death usually occurs secondary to immobility and malnutrition, which often lead to clinical manifestations of pneumonia or decubitus ulcers (Aderinwale et al., 2010; Alzheimer's Association, 2012). Currently, care for persons with AD is limited to exploratory or supportive treatments including both pharmacologic and nonpharmacologic interventions. Individuals with care and safety needs are often placed in facilities that will provide a safe and supportive environment as they become increasingly dependent in their activities of daily living throughout the course of the disease. Settings available may include assisted living facilities, nursing homes, dementia-specific care units, and hospice and palliative care services (National Institute on Aging, 2013).

Behavioral Symptoms in Alzheimer Disease (AD). Common behavioral symptoms in AD include sleeplessness, agitation, wandering, anxiety, apathy, anger and depression (Lyketsos et al., 2002; Mega, Cummings, Fiorello, & Gornbein, 1996; National Institute on Aging, 2013). These and other personality changes and behavioral symptoms may cause a person to seek clinical evaluation for AD or may emerge over the course of the disease (Petry, Cummings, Hill, & Shapira, 1988). Reisberg and colleagues (1987) were some of the early investigators to identify behavioral symptoms in AD. In a chart review of 57 outpatient individuals with AD,

58% of patients demonstrated significant behavioral symptoms. The most commonly identified behavioral symptoms in that sample included delusions, agitation, and sleep disturbance (Reisberg et al., 1987). Cummings and colleagues developed the Neuropsychiatric Inventory (NPI) to assess ten behavioral disturbances commonly occurring in persons with dementia, including: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, and aberrant motor activity (Cummings et al., 1994). Mega and others (1996) conducted a foundational study examining the same ten behaviors among persons with dementia. All ten behaviors were significantly increased in persons with AD compared with control subjects (Mega et al., 1996). Apathy emerged as the most common behavior and was exhibited by 72% of the individuals with AD (Mega et al., 1996). Agitation and aggression were also common behavioral symptoms in persons with dementia in an early study (Cohen-Mansfield, 1996). Agitated and aggressive behavioral symptoms may be expressed as physical aggression or striking out, physical agitation such as wandering or picking at things, verbal aggression or threats, and verbal agitation like repetitive questions or noises (Cohen-Mansfield, 1996).

In a publication based on results from the Cardiovascular Health Study, Lyketsos and colleagues (2002) found that 75% of participants with dementia had experienced at least one neuropsychiatric symptom in the past month. The most frequent behavioral disturbances among participants with dementia were apathy, depression, and agitation/aggression, with apathy most frequently displayed (Lyketsos et al., 2002). While apathy is a highly prevalent behavioral symptom among persons with AD, it is often under recognized (Benoit et al., 2008; Landes, Sperry, Strauss, & Geldmacher, 2001; Lerner, Strauss, & Sami, 2007; Lyketsos et al., 2002; Mega et al., 1996; Monastero et al., 2006; Robert, Mullin, Mallea, & David, 2010).

Apathy. There is a lack of clarity surrounding the conceptual definition of apathy in the literature. Apathy was originally defined as a lack of motivation (Marin, Biercrzycki, & Firinciogullari, 1991) but has more recently been characterized by diminished initiation, poor persistence, lack of interest, indifference, low social engagement, blunted emotional response, and lack of insight (Cohen-Mansfield, Dakheel-Ali, & Marx, 2009; Politis et al., 2004; Robert et al., 2010). For the purpose of this dissertation research, apathy is defined as a disorder of motivation with deficits in behavioral, emotional, and/or cognitive domains. Behavioral deficits in apathetic individuals might include diminished initiation or poor persistence (Landes et al., 2001; Lerner et al., 2007). Emotional deficits in apathetic individuals can include low social engagement or blunted emotional response (Landes et al., 2001; Lerner et al., 2007; Marin, 1996). Finally, cognitive deficits in apathetic individuals might include lack of interest or lack of insight (Landes et al., 2001; Lerner et al., 2007; Marin, 1996; Robert et al., 2002).

While apathy is a prominent behavioral symptom in persons with dementia, it may also manifest in persons with other neurologic conditions or related disorders. Several examples include persons with anoxic encephalopathy, cerebral neoplasms, chronic subdural hematoma, depression, head injury, stroke, Huntington's disease, schizophrenia, or Parkinson's disease (Lerner et al., 2007; Marin, 1996). Additionally, Robert and colleagues (2010) state that apathy and depressive symptoms are the most frequently observed symptoms of neuropsychiatric origin in mild cognitive impairment (MCI). Depression, apathy, and irritability were the most commonly exhibited neuropsychiatric symptoms among a subset of participants from the Cardiovascular Health Study exhibiting MCI (Lyketsos et al., 2002).

Apathy in Persons with Alzheimer Disease (AD). Apathy is a highly prevalent behavioral symptom in persons with AD, reportedly occurring in over 90% of persons with AD

across the disease trajectory with varying severity (Benoit et al., 2008; Mega et al., 1996). While common, apathy is often an under-recognized neuropsychiatric behavior in persons with AD (Landes et al., 2001; Lerner et al., 2007; Mega et al., 1996; Monastero et al., 2006; Robert et al., 2010). Apathy was the most frequently observed neuropsychiatric symptom among persons with dementia in a study of over 600 individuals (Lyketsos et al., 2002). The prevalence of apathy, however, was significantly less than 36%, as reported by Mega and colleagues (1996). To that end, the range of reported prevalence varies widely based on the measurement tool utilized to record apathy among persons with dementia. Apathy is not typically a transient behavioral symptom, but persists across the illness trajectory with varying severity (Benoit et al., 2008; Mega et al., 1996).

In addition to its high prevalence, the consequences of apathy for persons with AD are substantial. A longitudinal study reported that apathy was a significant predictor of accelerated cognitive, functional, and emotional decline in persons with AD (Starkstein, Jorge, Mizrahi, & Robinson, 2006). Apathy has a negative impact on several functional health outcomes and has been associated with poor functional performance among persons with questionable dementia, as well as in persons diagnosed with AD (Lam et al., 2010; Lam, Tam, Chiu, & Lui, 2008). Specific consequences of apathy for persons with dementia include physical deconditioning, failure of rehabilitation, decreased performance of activities of daily living, uncooperativeness with care, combativeness, and social isolation (Politis et al., 2004). Pronounced deficits in global cognition and instrumental abilities, as well as compromised nutritional status, exist in persons with apathy and AD (Benoit et al., 2008). Persons with AD who experience apathy may therefore require increased support and management.

Apathy presents particular caregiving challenges for family members, as persons with AD may be depressed, disengaged, or indifferent (Marin, 1996; Strauss & Sperry, 2002). In fact, caregivers of persons with dementia exhibiting apathy report significant levels of distress and caregiver burden (Kaufer et al., 2000; Sanders, Ott, Kelber, & Noonan, 2008). This caregiver burden may lead family members to more quickly institutionalize persons with AD, creating increased health care costs and utilization, and contributing to the substantial costs of caring for persons with AD to American society (Alzheimer's Association, 2012).

While apathy research remains in the early stages, emerging evidence supports apathy as a nurse sensitive outcome. Nonpharmacologic interventions show promise as symptom control modalities among persons with AD (Lerner et al., 2007; Politis et al., 2004; Wells & Dawson, 2000; Wood, Womack, & Hooper, 2009). In fact, nonpharmacologic interventions for behavioral symptoms in dementia have demonstrated effectiveness and may additionally serve to improve caregiver reactions to negative behavioral symptoms in dementia (Brodaty & Arasaratnam, 2012). To that end, meaningful engagement is a variable that can potentially be manipulated by nursing intervention in order to influence apathy among individuals with AD. Based on a conceptual analysis by Dykstra Goris (manuscript in development), meaningful engagement is defined as an event that takes place between two individuals, or an individual and an activity, in which there is 1) an outstanding need, 2) the individual is responsive/aroused, 3) there is positive emotional tone, and 4) the event is relevant, of good quality, of sufficient quantity, and is comprehensible to the individual.

Wells and Dawson (2000) demonstrated that nursing home residents with dementia can retain an array of capacities, including selected self-care, social, interactional, and interpretive abilities. Similarly, Wood and colleagues (2009) found that some individuals with AD remain

able to engage in social exchanges, participate in familiar activities, experience diverse emotions, and understand joy and humor. However, persons with dementia often become dependent on others to fully express these retained capacities (Landes et al., 2001; Wood et al., 2009). Individually tailored nonpharmacologic interventions may then effectively improve quality of life and reduce social isolation among persons with AD (Lerner et al., 2007). Specifically, regular one-on-one personal contact tailored to the individual's skill level or "personality style of interest" may lead to improvements in apathy and other neuropsychiatric disturbances in people with dementia (Kolanowski, Litaker, & Buettner, 2005; Kolanowski, Litaker, Buettner, Moeller, & Costa, 2011; Lam et al., 2010; Politis et al., 2004). Nurses should be encouraged to introduce sources of pleasure, interest, and stimulation to persons with apathy. Increased opportunities for socialization and nursing care to promote patient-centeredness and autonomy are recommended (Ishii, Weintraub, & Mervis, 2009). However, a better understanding of the measurement of apathy, etiology and risk factors for apathy, particularly genetic risk factors, is needed in order to inform the development and tailoring of these non-pharmacologic interventions.

Genetic Risk Factors for Apathy. Genetics play a role in the risk for AD (Corder et al., 1993; Pericak-Vance et al., 1991) and variability in clinical symptoms (Monastero et al., 2006; Schutte, Reed, DeCranes, & Ersig, 2011). Monastero and colleagues (2006) conducted a study examining the association between the *Apolipoprotein E (APOE) e4* genotype and neuropsychiatric symptoms in persons with AD. *APOE4* carriers showed a higher frequency of apathy than non-carriers, suggesting a relationship between the *APOE4* allele and apathy in persons with AD (Monastero et al., 2006). In a study by Schutte and colleagues (2011), single polymorphisms within the *Saitohin* and *APOE* genes demonstrated association with increased cognitive and functional impairment. The *APOE4* allele was also associated with increased

baseline levels of physical agitation in this twelve month repeated measures investigation of symptom variability among institutionalized persons with AD (Schutte et al., 2011).

Oxytocin (OT) is another candidate gene particularly relevant to the study of apathy. Multiple theories regarding OT exist, but OT may influence social behavior by promoting increased gaze to the eye region of the human face, promoting trust, or serving a role in social memory (Averbeck, 2010; Campbell, 2010). Studies have begun to consider a possible role of pathological OT signaling in psychiatric disorders like schizophrenia (Averbeck, 2010), autism spectrum disorders (Lerer et al., 2008) and Attention Deficit Hyperactivity Disorder (Park et al., 2010). Evidence from both human and animal studies provides strong rationale for exploring the extent to which deoxyribonucleic acid (DNA) variations within the *Oxytocin Receptor* (*OXTR*) gene influence the presence and severity of apathy in persons with AD.

Problem Statement

Despite the high prevalence and negative sequela associated with apathy, little is known about characteristics of persons with AD, including biologic factors that contribute to the presence and severity of apathy in persons with AD. The current knowledge gap prevents healthcare providers from properly identifying which individuals might be more prone to apathy and identifying how resident characteristics and social environmental factors impact the presence and severity of apathy in persons with AD, as well as subsequent functional outcomes. Further, the current knowledge gap limits the development of rigorous intervention studies to combat this problem. Therefore, a critical need exists to further examine apathy in persons with AD.

Purpose of the Study

The objective of this dissertation study was to examine the extent to which, after adjusting for AD severity, resident characteristics, including biological factors, and social

environment factors predict the severity of apathy in persons with AD as a foundation for future intervention research. Because OT was recently implicated as a moderator of human social behaviors with possible significance to social decision-making (Averbeck, 2010; Campbell, 2010), *OXTR* was examined as an important potential modifier in the prediction of apathy in persons with AD. The effect of apathy on functional status among this sample was also investigated, as supporting evidence exists for the deleterious effect of apathy on functional status in persons with dementia (Lam et al., 2008).

The dissertation project addressed the identified knowledge gap, providing a foundation for the development of rigorous nonpharmacologic intervention studies in the future. The investigator's long-term research goal is to conduct intervention studies designed to increase meaningful activity and social engagement in this vulnerable population of older adults with AD as a means to decrease apathy and improve their quality of life.

Specific Aims

Aim 1. Examine the extent to which individual characteristics (demographics and cognitive status) and social environment factors predict the severity of apathy in persons with AD, after adjusting for AD severity and *APOE4* status.

Hypothesis: More compromised cognitive status and less stimulating social environments are associated with increased severity of apathy in persons AD, when controlling for both severity of AD and *APOE4* genotype status.

Aim 2. Examine the extent to which variations in the *Oxytocin Receptor (OXTR)* gene are associated with apathy in persons with AD.

Hypothesis: Variants within the *Oxytocin Receptor (OXTR)* gene are associated with apathy in persons with AD.

Aim 3. Examine the extent to which severity of apathy influences functional status in persons with AD, after adjusting for AD severity

Hypothesis: More severe apathy is associated with decreased functional status in persons with AD, when controlling for severity of AD.

Study Design and Innovation

The dissertation study employed a cross-sectional correlational descriptive design to examine the extent to which interactions between individual and social environmental factors influence the presence and severity of apathy in persons with AD. *OXTR* was examined as an important potential modifier in the prediction of apathy in persons with AD. Particularly in persons in more advanced stages of AD, exploring a candidate gene marker for apathy is extremely innovative. The dissertation was part of an ongoing parent study (Schutte, Maas, & Buckwalter, 2003; Schutte et al., 2011) of gene-environment interactions in the symptoms of AD, in which persons with a diagnosis of possible or probable AD were recruited from the community and long-term care facilities by way of convenience sampling. A modified version of the Need-Driven Dementia-Compromised Behavior (NDB) model (Algase et al., 1996) provided the theoretical foundation for the dissertation project, as the NDB model presents a unique way of thinking about problematic neuropsychiatric behaviors in persons with dementia. It may be that persons with dementia demonstrate apathy as the expression of an unmet goal or need, adhering to the definition of a NDB by Algase and colleagues (1996).

Summary

This dissertation research provided a unique opportunity to examine apathy, a common and problematic behavioral symptom in persons with AD, building upon the exiting literature related to broader studies of behavioral symptoms in AD. This is a novel study, being one of the first to

examine the *Oxytocin Receptor (OXTR)* gene as related to apathy. To that end, this dissertation study allowed for the examination of both predictors and consequences of apathy, providing a platform for future research. The investigator's long-term research goal is to conduct intervention studies designed to increase meaningful activity and social engagement in this vulnerable population of older adults with AD as a means to decrease apathy and improve their quality of life.

CHAPTER 2: THEORETICAL FRAMEWORK

Human beings have a set of basic needs. Often these basic needs are considered to be necessities like food, water, clothing and shelter. It may be argued, however, that some degree of relational interaction is also necessary in a human life. This proposal is based upon the assumption that meaningful engagement is one of these basic human needs and is relevant to the study of apathy in persons with Alzheimer Disease (AD). The purpose of this chapter is to 1) discuss the concept of apathy, 2) discuss apathy in the context of related concepts, such as emotion and meaning, 3) describe and evaluate the Need-Driven Dementia-Compromised Behavior (NDB) model (Algase et al., 1996) as the underlying framework for the proposed dissertation study, and 4) introduce an adapted version of the model.

Apathy

The literature demonstrates the lack of a standard research or clinical definition of apathy, which makes identifying, studying, and treating apathy among persons with AD more difficult (Landes et al., 2001; Lerner et al., 2007). Much of the challenge lies in distinguishing the loss of motivation from loss of ability, which is particularly difficult in a cognitively compromised population (Landes et al., 2001). Clinical diagnostic criteria for apathy were first proposed by Marin (1996), who states, "the essential meaning of apathy is lack of motivation" (p. 304). The distinguishing features of apathy, according to Marin (1996), include the simultaneous effect on three aspects of goal-directed behavior: activity, cognition associated with goals, and emotional responses associated with these activities and goals. Marin (1996) also emphasizes conscious and intentional mental activity, as well as the unconscious psychological and biological processes involved in goal-directed behavior. He attempts to define true apathy as a distinct *syndrome* that cannot be attributed to other co-morbid conditions. He acknowledges that apathy

may also be viewed as a *symptom* in the context of various clinical syndromes. Marin, Biercrzycki and Firinciogullari (1991) made an early attempt to operationalize apathy with the development of the 18-item Apathy Evaluation Scale (AES).

The AES was developed to, "quantify and characterize apathy in adult patients" (Marin et al., 1991, p.144) and may be used to evaluate patients suffering from what Marin calls apathetic syndrome. The AES may also be used to evaluate patients experiencing apathy as a symptom of some other condition like delirium, dementia or depression. Multiple raters may complete the AES and several versions exist, including clinician rated (AES-C), informant rated (AES-I), and self-rated (AES-S) versions (Marin et al., 1991). The AES consists of 18 items that are scored on a four-point Likert scale. Higher scores indicate more severe apathy (Leentjens et al., 2008; Marin et al., 1991). Marin and colleagues (1991) report satisfactory measures of reliability for each version of the AES. Specifically, internal consistency for the AES-C was reported as Cronbach's alpha 0.90, test-retest reliability as r=0.88, and inter-rater reliability as Kappa=0.94 (Marin et al., 1991). Internal consistency for the AES-I was reported as Cronbach's alpha 0.94 with a test-retest reliability of r=0.94 (Marin et al., 1991).

Starkstein (2000) uses Marin's (1996) conceptualization of apathy as the "absence or lack of feeling, emotion, interest, concern, or motivation" (p. 135), but suggests a broadening of the criteria for apathy so that patients with apathy in the context of depression and other diagnoses may also be identified. He argues that whether apathy is a single symptom or a behavioral syndrome remains unclear. Starkstein's work found that apathy was significantly more common among patients with AD than among age-matched healthy controls. He also found that patients with AD and apathy were unaware of the magnitude of the cognitive and behavioral changes

they were experiencing, as evidenced by significantly different scores on separate evaluations of patients with AD and their caregivers (Starkstein, 2000).

Lerner and colleagues (2007) fail to define apathy, but offer that apathy encompasses, "diminished initiation, poor persistence of action or thought, lack of interest, indifference, low social engagement, blunted emotional response, and lack of insight" (p.15). Lerner and colleagues further assert that apathy causes less patient distress than some other neuropsychiatric symptoms. For that reason, apathy has received little attention unless families or healthcare providers recognize apathy and choose to pursue its treatment (Lerner et al., 2007).

The definition of apathy as lack of motivation has been challenged. For example, Levy and Czernecki (2006) criticize Marin's (1996) definition of apathy as a lack of motivation, because motivation is a concept stemming from behavioral and social psychology. For this reason it is, ". . . difficult to propose a consensus on its [apathy] definition and overall to transfer this concept to the level of its physiopathological basis" (Levy & Czernecki, 2006, p.VII55). Levy and Czernecki propose a definition of apathy as a, "quantified and observable behavioral syndrome consisting in a quantitative reduction of voluntary (or goal-directed) behaviors" (p. VII54), so that apathy occurs when areas of the brain generating control and voluntary actions are altered (Levy & Czernecki, 2006). van Reekum and colleagues (2005) suggest that apathy be defined as, "an absence of responsiveness to a stimulus, with requirement that this lack of responsiveness be demonstrated by a lack of self-initiated action" (p. 8), incorporating initiation as a central component of apathy (Ishii et al., 2009; van Reekum, Stuss, & Ostrander, 2005). Ishii and colleagues (2009) believe that there is no clear consensus on the most appropriate definition of apathy but that it may present, "as a syndrome in which lack of motivation is a

predominant feature and cannot be attributed to intellectual impairment, emotional distress, or diminished level of consciousness" (p.381).

This lack of conceptual clarity prompted the commission of a task force to propose diagnostic criteria for apathy (Robert et al., 2010). As a result, three core domains of apathy - behavior, cognition, and emotion – were established (Robert et al., 2010). The domains are consistent with previously published literature and based on the idea that a change in individual motivation can be measured by examining a patient's response to internal or external stimuli. Within each of the three domains, both an internal "initiation" symptom and external "responsiveness" symptom must be present to meet diagnostic criteria for apathy (Robert et al., 2010).

For the purpose of this dissertation research, apathy is defined as a disorder of motivation with deficits in behavioral, emotional, and/or cognitive domains. Behavioral deficits in apathetic individuals might include diminished initiation or poor persistence (Landes et al., 2001; Lerner et al., 2007). Emotional deficits in apathetic individuals can include low social engagement or blunted emotional response (Landes et al., 2001; Lerner et al., 2007; Marin, 1996). Finally, cognitive deficits in apathetic individuals include lack of interest or lack of insight (Landes et al., 2001; Lerner et al., 2007; Marin, 1996; Robert et al., 2002).

Apathetic symptoms do not occur in isolation, but must be viewed in relationship to the cognitive, psychosocial, and physical and social environment of the individual. A solely disease-oriented approach fails to consider the environmental impact on persons with AD. Wood, Womack, and Hooper (2009) compared time use, affect, and routine activity among residents on two AD special care units. Participants from both special care units were observed to be capable of conversational behavior, but spent their days mostly in silence (Wood et al., 2009).

Additionally, persons with dementia in nursing homes are reportedly least likely among nursing home residents to be engaged and often spend considerable time doing nothing at all (Hill, Kolanowski, & Kurum, 2010).

Daily portraits of time use and apparent affect suggested to Wood and colleagues (2009) that cognitive, social, emotional, ambulatory, and other physical capacities were maintained, but infrequently expressed each day, regardless of facility. Individuals with AD in that sample remained able to engage in social exchanges, participate in familiar activities, experience diverse emotions, and understand joy and humor. Wells and Dawson (2000) also demonstrated that nursing home residents with dementia retain an array of capacities, including selected self-care, social, interactional, and interpretive abilities. According to the literature, though, residents often become dependent on others to fully express these retained capacities (Landes et al., 2001; Wood et al., 2009). Initiation of an activity or conversation from an outside source may be necessary for the expression of diverse emotions or the engagement in a social exchange, as apathy negatively impacts motivation. Additionally, persons with dementia and apathy may ineffectively communicate unmet needs, which points to outstanding care needs and a severely compromised quality of life.

Apathy in the Context of Emotion and Meaning

Meaningful engagement is a variable that can potentially be manipulated in order to influence apathy in individuals with AD. Based on a conceptual analysis by Dykstra Goris (manuscript in development), meaningful engagement is defined as an event that takes place between two individuals, or an individual and an activity, in which there is 1) an outstanding need, 2) the individual is responsive/aroused, 3) there is positive emotional tone, and 4) the event is relevant, of good quality, of sufficient quantity, and is comprehensible to the individual.

According to Oxford Dictionaries online, *meaning* is defined as, "important or worthwhile quality; purpose" to an event or an exchange. *Engage* is defined as, "occupy, attract, or involve (someone's interest or attention)" (Oxford University Press, 2013). Psychology literature suggests that persons with dementia may be unable to fully participate in meaningful engagement, due to an inability to effectively experience or express emotion secondary to impaired cognition. Early work by Lazarus (1982) submits that emotions, which are involved in meaningful engagement, are cognitively mediated. This work implies that persons with AD may not be able to *experience* meaningful engagement (Lazarus, 1982).

Oxford Dictionaries online define *emotion* as, "a strong feeling deriving from one's circumstances, mood, or relationships with others" (Oxford University Press, 2013). *Emotion* is an "instinctive or intuitive feeling as distinguished from reasoning or knowledge" (Oxford University Press, 2013). If emotion is unique from reasoning or knowledge, it clearly remains in cognitive decline. It is instinctive. It seems that emotion may not, then, be the same as meaning. Must one reason in order to assign *meaning*, an "important or worthwhile quality; purpose" (Oxford University Press, 2013) to an event or an exchange? What are the implications in dementia, specifically?

The Model of Psychological Well-Being in Advanced Dementia (Volicer, Hurley, & Camberg, 1999) addresses the gradual decline in ability among individuals with dementia, "to *express* affect and objective indicators of psychological well-being" (p. 83). According to the model, the inability to initiate meaningful activities and a lack of environmental engagement represent significant consequences of dementia. The lack of meaningful engagement may bring about negative consequences, including apathy, agitation and depression (Volicer et al., 1999).

The Model of Psychological Well-Being in Advanced Dementia includes three continuums: Happy-Sad, Calm-Agitated, and Engaged-Apathetic (Volicer et al., 1999). The Happy-Sad continuum may be recognized based on an individual's facial expression. The Calm-Agitated continuum is expressed by individuals via bodily movements and vocalization. Thirdly, the Engaged-Apathetic continuum is measured by the degree of an individual's involvement with his or her environment. Volicer and colleagues (1999) characterize persons who are happy, calm and engaged with the environment as those with the most optimal psychological well-being. The contrasting absence of psychological well-being manifests in agitation, unhappiness and apathy. Optimal psychological well-being in persons with dementia may then be best achieved by the provision of appropriate and meaningful activities (Volicer et al., 1999).

Yao and Algase (2008) frame meaningful engagement through the lens of motivation theory. The Locomoting Responses to Environment in Elders with Dementia (LRE-EWD) model integrates, "the role of emotion with that of cognition in explicating a person-environment dynamic supporting wandering and other dementia-related disturbances" (p. 106). Yao and Algase (2008) acknowledge that one of the most challenging pursuits in the fields of psychology and behavioral neuroscience has been to better understand the human brain processing of information and emotion to produce complex behaviors. Based on pioneering work, Yao and Algase (2008) cite that "Scholars now agree no meaningful thoughts, actions, or environmental encounters occur without affect" (p. 108). The LRE-EWD model theorizes that brain pathways, responsible for processing emotions, are relatively spared in dementias like AD (Yao & Algase, 2008).

It may be that emotional needs must be met through circumstances, mood, or relationships with others in order for one to experience meaning. In a reciprocal fashion,

outstanding emotional needs may come from a desire for meaning. Emotion persists in apathetic individuals with AD. Persons with dementia experiencing apathy may not be able to initiate the appropriate behavior one might expect from an individual without cognitive impairment. The blunted emotional response characteristic of persons with apathy may lead caretakers and family members to believe that individuals with AD are no longer able to feel or fulfill emotional needs. However, the literature suggests this is not the case.

Harmer and Orrell (2008) completed an extensive literature review and qualitative analysis on meaningful activity for persons with dementia. It was determined that humans seek meaningful activity by nature and use meaningful activities to structure life (Harmer & Orrell, 2008). Individuals suffering from various stages of dementia were able to participate in several activities. The qualitative analysis revealed that residents found meaning in, "Activities that addressed their psychological and social needs, which related to the quality of the experience of an activity rather than specific types of activities" (Harmer & Orrell, 2008, p.548). Authors found that "reminiscence, music, family and social activities", as well as "activities related to the individual", were particularly meaningful to residents suffering from dementia in a long-term care facility (Harmer & Orrell, 2008, p.556). In contrast, facility staff and family caregivers viewed activities that maintained physical ability as most meaningful in the lives of the persons with dementia (Harmer & Orrell, 2008). Therefore, meaningful activities may be perceived differently among persons with dementia and their caregivers. However, meaningful activities are useful in making a positive impact in the lives of individuals with dementia. Wood and colleagues (2009) state, "Spending time doing things that matter is also associated with a greater balance of positive as opposed to distressing emotions, or apathy, across the day" (p. 339). Environmental and social stimulation, preferably stimulation specifically oriented to the

individual's own interests, is an important component of research related to apathy, emotion and meaning.

Need-Driven Dementia-Compromised Behavior (NDB) Model

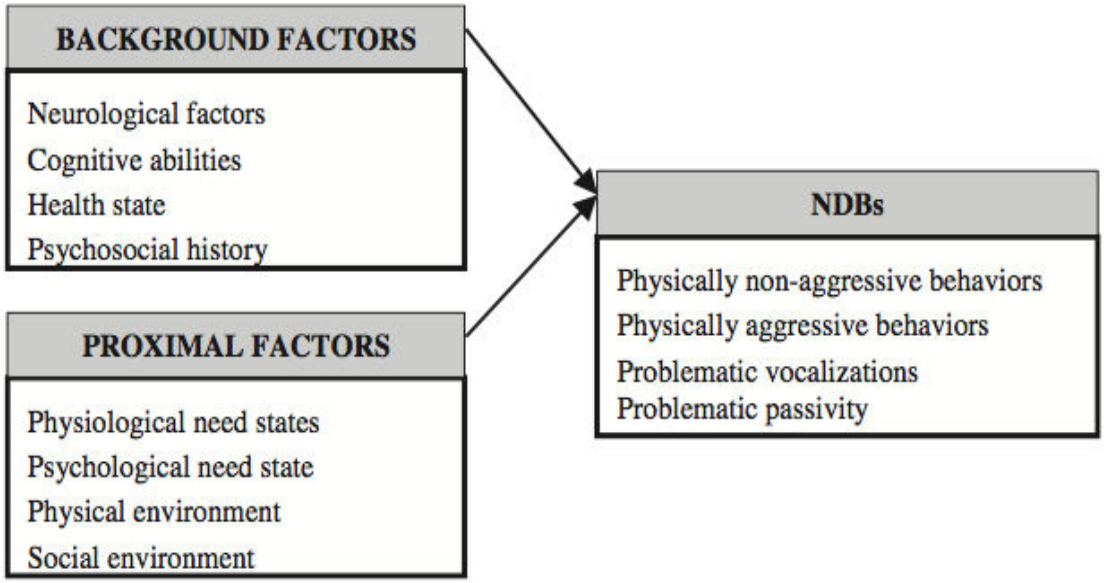
Historical Development. Walker and Avant describe a theory as a useful and internally consistent group of relational statements that help to present a systematic view of some phenomenon (Walker & Avant, 2005). The Need-Driven Dementia-Compromised Behavior (NDB) model (Algase et al., 1996) is helpful in considering apathy and basic needs among persons with AD. The NDB model originated from motivational theory and views persons as an element of the environment (Algase et al., 1996). Additionally, the NDB model is a middle-range theory originating from the nursing discipline (Kolanowski et al., 2005). Whall and Kolanowski (2004) note that the model displays similarities to theoretical frameworks rooted in developmental psychology.

Description of the Need-Driven Dementia-Compromised Behavior (NDB) Model. The NDB model (see Figure 1) presents a new way of thinking about negative or problematic behaviors in persons with dementia. The original model arose from nursing practice and a desire to re-frame caregiver thinking. It presents an insightful and less pejorative view of "problematic" behaviors in persons with dementia as expressions of unmet goals or needs (Algase et al., 1996). Three major concepts in the NDB model include background factors, proximal factors, and need driven behaviors (NDB).

Algase and colleagues (1996) describe background factors as fairly static in the lives of individuals with dementia. The concept of background factors includes neurological status, cognitive abilities, general health state, and psychosocial state (e.g., premorbid social personality). The NDB model theorists suggest that background factors may be difficult to

change or influence with nursing intervention, but that it is important to have knowledge of background factor variables, as they are helpful in identifying persons at risk for displaying NDB.

Figure 1. *The Need-Driven Dementia-Compromised Behavior Model (Algase et al., 1996)



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Algase and colleagues (1996) describe the concept of proximal factors as encompassing changeable factors in the immediate environment of individuals with dementia. Social environment, physical environment, psychological need state and physiological need state are contained within the major concept of proximal factors. According to Algase and colleagues (1996), the social environment encompasses social contacts, personal network, and caregivers. Proximal factor variables, more imminently than background factor variables, may propel an individual with dementia to display NDB, as proximal factors represent dynamic and changing needs and states within a cognitively impaired person.

The NDB model focuses on the central concept of NDBs among persons with dementia. The NDB theorists (1996) conceptualize that, "NDBs constitute the most integrated and meaningful response possible, given limitations imposed by a dementing condition, strengths preserved from the person's basic abilities and personality, and constraints, challenges, or supports offered by the immediate environment" (p.11). NDBs are theoretically assumed to be the result of interactions between relatively stable background factors or individual characteristics and less stable proximal factors or environmental triggers. Algase and colleagues (1996) posit that NDBs originate as the pursuit of a goal or expression of an unmet need in persons with dementia. Knowledge is generated by, "considering their [NDBs] purpose or meaning to persons who display them" (p. 10). The original NDB model focuses mainly on wandering, vocalizations, and agitation/aggression as NDBs in persons with dementia. Whall and Kolanowski (2004) have since included problematic passivity, which is closely conceptually related to apathy, as a NDB within the NDB model (Whall & Kolanowski, 2004).

Evaluation of the Need-Driven Dementia-Compromised Behavior (NDB) Model.

Fawcett (2005) provides a useful framework for analysis and evaluation of nursing theories. Components of theory analysis include assessment of the scope, context, and content of the theory. According to Fawcett (2005), theory evaluation must address significance, internal consistency, parsimony, testability, empirical adequacy and pragmatic adequacy of a model (Fawcett, 2005), in this case the NDB model.

Analysis.

Theory scope and context. In order to properly analyze a nursing theory, one must consider the theory scope, theory context, and theory content (Fawcett, 2005). The scope of the NDB model is the explanation of behaviors of persons with dementia as expressions of unmet

goals or needs. With regard to theory context, the NDB deals with human beings as an element of the environment (Algase et al., 1996). Important philosophical claims on which the theory is based include: 1) Behaviors of persons with dementia express or embody unmet goals or needs; 2) NDBs reflect the interaction of background and proximal factors found within a cognitively impaired person, within his or her immediate environment, or both; 3) NDBs often represent the most meaningful response possible for a person with dementia; and 4) Elements of the NDB model are sensitive to nursing intervention (Algase et al., 1996). The NDB theorists (1996) specify that reducing and responding to NDBs results in more humane treatment and improved quality of life among individuals suffering from dementia.

Theory content. Theory content analysis must address both concepts and propositions of a given nursing theory (Fawcett, 2005). Propositions represent the relationships linking major concepts (See Description of the Need-Driven Dementia-Compromised Behavior [NDB] Model) within a model (Fawcett, 2005). Major concepts must then relate to each other in some way to make the phenomenon present (Walker & Avant, 2005). Algase and colleagues (1996) propose that background factors and proximal factors interact to produce the NDB phenomenon in persons with dementia. For example, specific physiological need states, conceptualized as proximal factors, such as fatigue, hunger, or pain may induce NDB (Algase et al., 1996). Sleep patterns are also described as proximal factors that may interact with background factor variables to produce NDB. Based on cognitive ability, a background factor, and physiological or psychological need states (proximal factors), NDBs may be the most integrated response a person with AD can muster. This response may be especially true of persons with AD who have diminished verbal capacity, common in more advanced stages of AD.

Algase and colleagues (1996) cite that the number of NDBs significantly increases with greater cognitive impairment. Authors suggest that wandering, a main focus of the NDB model may arise from the interaction between background factors and intermittent feelings of anxiety, frustration, or boredom (proximal factors). Interestingly, the NDB model theorists state that wandering and aggressive behaviors, like screaming, are associated with greater time alone. Greater time alone is a manifestation of the social environment, represented by the proximal factors major concept. Similarly, it may be that the overall level of agitated behaviors displayed by an individual with dementia is related to lacking intimacy in the social network (Algase et al., 1996).

Evaluation.

Significance. The NDB model adds significantly to the conceptualization of behavioral symptoms in dementia. The model is relevant to nursing practice, as the original question stemmed from patient interaction, and the nursing discipline is credited with its origin. Previously, caregivers referred to repeated vocalizations, wandering, and agitation or aggression among persons with dementia as "problematic", "disturbing", or "disruptive" (Algase et al., 1996). The NDB model instead defines these behaviors as NDBs and considers them from the perspective of the individual with dementia. Metaparadigm concepts and propositions and philosophical claims on which the theory is based are explicitly addressed, further contributing to the significance of the NDB model (Fawcett, 2005).

Internal consistency. Internal consistency requires congruence among philosophical claims, the conceptual model and concepts and propositions stemming from the model, and is an important characteristic of high-quality theory (Fawcett, 2005). The NDB model is clear in both its definition and consistent use of major concepts. Each major concept is explicitly defined, and

consistent language is used throughout the theory. The NDB model, however, does not demonstrate complete structural consistency. Algase and colleagues (1996) state that background and proximal factor variables interact to produce NDB in persons with dementia, but this is inconsistent with the visual representation of the model (See Figure 1). Background factor variables and proximal factor variables appear to independently influence NDB in the visual representation of the model. The concept map lacks an arrow connecting the major concepts of background factors and proximal factors, which fails to indicate a reciprocal relationship between the two major concepts as represented in the textual description of the model.

Parsimony. For a nursing theory to be parsimonious, it must be stated in the most economical way without oversimplifying the phenomena of interest (Fawcett, 2005). The NDB model theorists propose three major concepts including background factors, proximal factors and NDB. Relationships among them are stated concisely. Though few major concepts are proposed, the major concepts introduced by Algase and colleagues (1996) are adequate for the phenomena being considered. Algase and colleagues (1996) sufficiently consider contributors to NDB in the form of several variables encompassed within the background factor and proximal factor concepts. They use an economical strategy for introducing a number of variables contributing to NDB. Several variables contributing to apathy are discussed in the original publication, though confounders in the measurement of NDBs are not thoroughly discussed.

Testability. The NDB lends itself well to testing, with an obvious intent for nursing research implementation upon initial development. Algase and colleagues (1996) suggest that researchers use the NDB model to better identify cognitively impaired persons at risk for NDB and to isolate needs that are most likely to precipitate NDBs. The goal is that such knowledge would allow researchers to develop and test targeted intervention strategies by specifically

modifying the relevant proximal factor variables for individuals exhibiting a particular NBD (Algase et al., 1996). The NDB model also includes sub-concepts with operational definitions for direct empirical testing (Fawcett, 2005). The Ambiance Scale (AS) has been developed to aid in evaluation of the social environments of persons with dementia (Algase et al., 2007). The Algase Wandering Scale, a 28-item questionnaire based on five dimensions of wandering, offers an operational definition of wandering as a NDB and contributes to further empirical testing of wandering (Algase, Beattie, Bogue, & Yao, 2001).

Empirical adequacy. For a theory to demonstrate empirical adequacy, theoretical assertions must be consistent with empirical evidence (Fawcett, 2005). A search of the literature yields multiple studies that demonstrate empirical evidence based on the NDB. For example, Kolanowski, Litaker, and Buettner (2005) designed and tested the efficacy of recreational activities derived from the NDB model. The NDB-derived activities were matched to skill level only, personality "style of interest" only, or a combination of both, in order to respond to the behavioral symptoms of dementia. Kolanowski and colleagues (2005) define personality "style of interest" as an individual's disposition toward meeting the inherent need for activity in a particular manner. Examples include extraversion and openness (Kolanowski et al., 2005). In another study, multiple regression models revealed that cognitive functioning, activities of daily living, race, gender and resident pain as reported by certified nursing assistants, were associated with NDBs among 161 nursing home residents with dementia (Norton, Allen, Snow, Hardin, & Burgio, 2010).

Pragmatic adequacy. A nursing theory with pragmatic adequacy must be applicable in the real world of nursing practice (Fawcett, 2005), and this is the case for the NDB model. It is generally feasible to implement practice protocols derived from the NDB model, and theory-

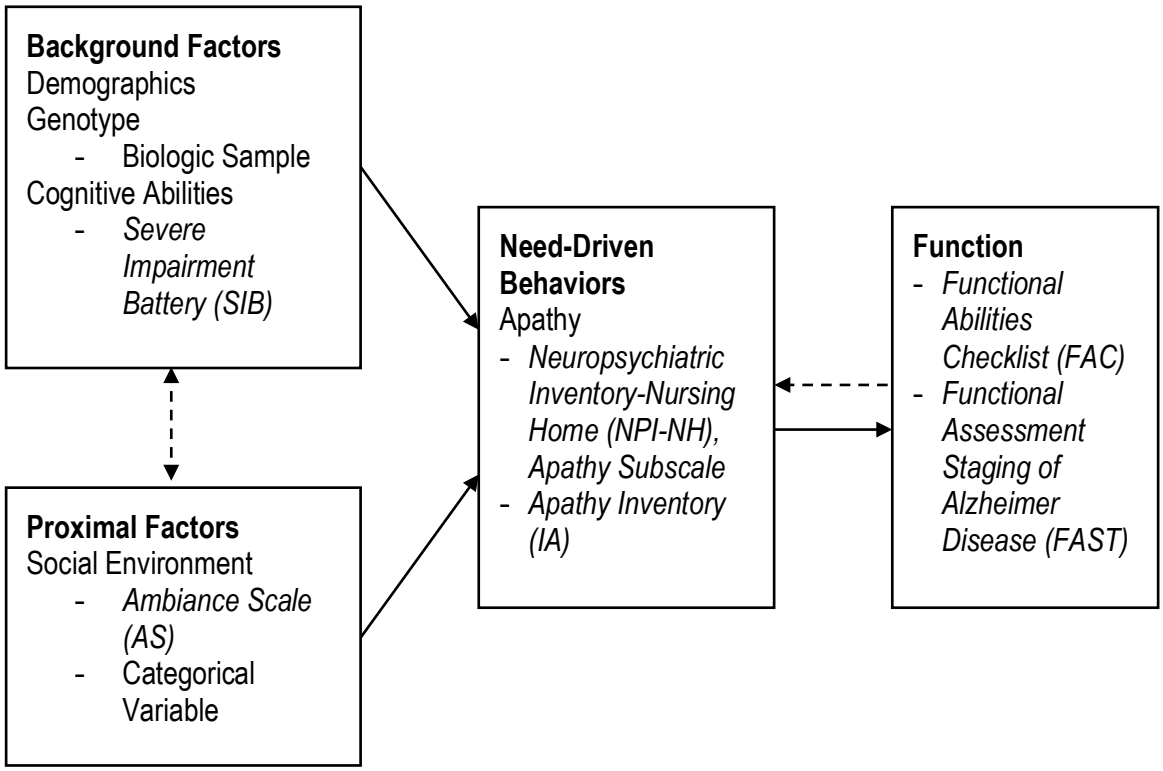
based nursing actions are compatible with expectations for nursing practice (Fawcett, 2005). To that end, the University of Iowa has published practice guidelines in order to assist nurses in utilizing the NDB model at the bedside (Smith, 2009). Colling (1999) specifically used the NDB model for clinical application to address passive behaviors in dementia. She identified that passive behaviors in individuals with dementia can be identified as disruptive and adequately assessed using the NDB model (Colling, 1999). To that end, specific nursing assessments for passivity in persons with dementia should include evaluation for various medical conditions, assessment of current medications, and examination of situations or stimuli that may provoke withdrawal (Colling, 1999). The knowledge that nursing interventions promoting interactions between individuals and the environment may result in positive therapeutic outcomes is a helpful contribution to the science (Colling, 1999). This investigation of passivity using the NDB model may be built upon using the concept of apathy, which is closely conceptually related.

Adapted Model for Dissertation Study

The theoretical framework used for this dissertation study is an adaptation of the Need-Driven Dementia-Compromised Behavior Model (NDB) (Algase et al., 1996) (See Figure 2). The NDB model is useful in considering apathy in dementia, especially because it has been used to examine problematic passivity as a NDB in persons with dementia (Colling, 1999; Whall & Kolanowski, 2004). The NDB model offers a fresh conceptualization of apathy in persons with dementia. Rather than viewing apathy as problematic, disturbing, or disruptive, the NDB model suggests regarding this behavior as the expression of an unmet goal or need (Algase et al., 1996). Perhaps apathy, a NDB, may be due to too little or too much stimulation in an individual's social or physical environment. The individual might also be attempting to convey a physiological, or more likely a psychological need, when demonstrating apathetic or passive behavior.

Function is included in the adapted model as a downstream sequela of apathy, based on published evidence of the relationship between apathy and functional status (Benoit et al., 2008; Boyle et al., 2003; Lam et al., 2006). According to Gomar, Harvey, Bobes-Bascaran, Davies, and Goldberg (2011), everyday function refers to "the self-initiated ability to perform those basic and complex behaviors necessary to live independently in the community" (p. 916). Apathy is associated with more pronounced deficits in global cognition and everyday life and instrumental abilities among persons suffering from mild to moderate stages of AD (Benoit et al., 2008) and poorer functional performance among those with AD (Lam et al., 2008). It may also be possible to predict functional impairment in mild to moderate AD based on executive dysfunction and the presence of apathy (Boyle et al., 2003). While this dissertation work is based on a descriptive design, one could utilize the NDB model to design an intervention study by manipulating proximal factor variables in order to better understand the impact of apathy and passivity on NDB in dementia, including the downstream impact of apathy on function.

Figure 2. *Adapted Model for use in Dissertation Study: Apathy, Genetics, and Functional Status in Persons with Alzheimer Disease



Note: Dashed arrows indicate relationships not examined as part of this dissertation study

CHAPTER 3: REVIEW OF THE LITERATURE

Alzheimer Disease (AD)

History of Alzheimer Disease (AD). Alzheimer Disease (AD) was first described by Alois Alzheimer, a German physician, over one hundred years ago (Maurer, Volk, & Gerbaldo, 1997). In his personal journals, he described the pathology and behavioral symptoms exhibited by Auguste Deter, who was housed in a Frankfort hospital. Deter first presented with impaired memory, aphasia, and disorientation. Eventually, her condition progressed to include further loss of cognitive function and hallucinations (Maurer et al., 1997; National Institute on Aging, 2013). Alzheimer documented Deter's decline, dissected her brain post-mortem, and presented her case in 1906 (Maurer et al., 1997). Deter's case was described elsewhere by Fisher, Bonfiglio and Perusini, but Kraepelin introduced the eponym Alzheimer's Disease (AD) in the eighth edition of his book Psychiatrie in 1910 (Alzheimer's Association, 2012; Maurer et al., 1997). Alois Alzheimer's second published case detailed the clinical history of a 56-year-old man (Graeber et al., 1997).

In the 1960s, cognitive measurement scales were developed, providing an opportunity to examine the relationship between cognitive decline and the number of plaques and tangles in the brain (Alzheimer's Association, 2012). At that time, AD was also recognized as distinct from the normal aging processes. In 1976, neurologist Robert Katzman identified AD as the most common cause of dementia, raising awareness of AD as a public health challenge (Alzheimer's Association, 2012; Katzman, 1976).

Alzheimer Disease (AD) Phenotype. The broad clinical phenotype of AD is characterized by dementia, or a progressive deterioration in global cognitive ability. In fact, AD is the most common cause of irreversible dementia (National Institute on Aging, 2013) and is

discussed in relationship to other neuropsychiatric disorders in a review article by Schutte, Davies, and Goris (2013). Classifications for AD include mild, moderate, and severe. The disease most often manifests after age 60, recognized as late-onset AD, impacting nearly every facet of daily life (National Institute on Aging, 2013). In contrast, the onset of AD has been reported as early as age 24 (Campion et al., 1999). Symptom presentation prior to age 65 has been classified as the 'early-onset' form of the disease. The average duration of AD is eight to ten years, with a range from one to twenty-five years (Bird, 2010).

The classic neuropathologic features of amyloid plaques and neurofibrillary tangles result in the progressive destruction of neurons in the cortex and limbic structures of the brain, impacting areas responsible for learning, memory, behavior, emotion, and reasoning (Aderinwale et al., 2010). AD is characterized, initially, by subtle and often poorly recognized memory failure. Memory loss becomes increasingly severe, and eventually incapacitating (Aderinwale et al., 2010; Bird, 2010). AD manifests in cognitive, functional, and behavioral difficulties. However, there is a great deal of variability among individuals with AD. Common clinical features of AD include: confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations (Bird, 2010).

Epidemiology of Alzheimer Disease (AD). About 5.4 million Americans currently suffer from AD (Alzheimer's Association, 2012). The United States is projected to experience growth in its older population at a rapid rate, partially due to the number of aging baby boomers, defined as persons born between 1946 and 1964 (U. S. Census Bureau, 2010). The United States Census Bureau estimates that 88.5 million Americans will be aged 65 and older in the year 2050. Paralleling the number of older Americans, the number of persons with AD will dramatically increase in the future unless curative or preventative measures are developed (Hebert, Weuve,

Scherr, & Evans, 2013). Based on 2010 United States Census data, it is estimated that AD prevalence in the year 2050 will be 13.8 million, with 7 million persons aged 85 or older projected to suffer from AD (Hebert et al., 2013). Similarly, the Alzheimer's Association estimates that the number of individuals with AD may reach 16 million in 2050. AD is the sixth-leading cause of death in the United States, with 15 million Americans providing unpaid care to individuals with AD and other dementias (Alzheimer's Association, 2012).

The current overall lifetime risk for any individual to develop dementia is approximately 10%-12% (Bird, 2010). If a family has a single occurrence of AD, first-degree relatives (i.e. parents, siblings, offspring) have approximately a 15%-30% cumulative lifetime risk of developing AD. In genetic counseling situations, this is typically reported as 20%-25% risk (Bird, 2010). The National Institutes of Health estimate that about 25% of all AD is familial, defined as two or more persons in a family exhibiting AD. Of this familial AD, approximately 95% is late-onset (age >60-65 years) and 5% is early-onset (age <65 years) (Bird, 2010).

Gender and racial differences exist in the prevalence of AD. AD and other dementias are most common among females (Alzheimer's Association, 2012). This difference may primarily be explained by the fact that on average, women live longer than men. Based on data from the Aging, Demographics, and Memory Study, it is estimated that 16% of women and 11% of men over age 71 have AD or other dementias (Plassman et al., 2007; Seshadri et al., 1997). With regard to ethnicity, Latinos and African Americans have a higher lifetime risk for AD than their Caucasian counterparts, which may be due to their relatively higher rates of vascular disease (Alzheimer's Association, 2012).

Complex Etiology of Alzheimer Disease (AD). AD is a multifactorial disease, with strong genetic components to both early-onset and late-onset AD (Aderinwale et al., 2010;

Maurer et al., 1997). The cause of AD is likely a complex combination of genetic influences and environmental exposures that have accumulated over the lifespan (Gatz, Reynolds, Finkel, Pedersen, & Walters, 2010). When one considers both epidemiologic and clinical studies over the past two decades, the only robust and undisputed risk factors for AD are age and carrying the *Apolipoprotein E (APOE) e4* allele (Corder et al., 1993; Dartigues & Feart, 2011).

Mutations in three genes have been implicated in causing AD among some families exhibiting early-onset AD by way of an autosomal dominant inheritance pattern (Goate et al., 1991; Levy-Lahad et al., 1995; Mullan et al., 1992). These include the *Presenilin 1 (PSEN1)* and *Presenilin 2 (PSEN2)* genes, which are located on chromosomes 14 and 1, respectively, as well as the *Amyloid Precurson Protein (APP)* gene (Goate et al., 1991; Levy-Lahad et al., 1995; Mullan et al., 1992). When altered *PSEN* genes exist, ineffective PSEN proteins are subsequently produced. PSEN proteins are components involved in the γ-secretase machinery, which function to cleave APP into the smaller sections of the Aß protein and are involved in protein trafficking (Campion et al., 1999).

The vast majority of AD cases are late-onset, after age 60 (National Institute on Aging, 2013). While the *APOE* gene is polymorphic with three major isoforms, *APOE3, APOE4, and APOE2* (Strittmatter et al., 1993), *APOE4* has the most consistent evidence for increasing the risk of late-onset AD (Pericak-Vance et al., 1991). The *APOE* gene is located on the long arm of chromosome 19 and consists of four exons and three introns, with a total of 3597 base pairs (Lewis, 2010).

The important role of *APOE* was first identified through linkage analysis by Pericak-Vance of Duke University (Pericak-Vance et al., 1991). Later, Corder and colleagues (1993) evaluated members of 42 families with late-onset AD. The proportion of affected individuals

increased with the number of *APOE4* alleles, demonstrating a highly significant additive trend (Corder et al., 1993). Specifically, individual risk for AD increased by a factor of 2.84 for each additional *APOE4* allele. When the relationship between *APOE4* and age of onset was examined, each additional *APOE4* allele shifted onset to a younger age (Corder et al., 1993). Survival distributions examined survival of persons with 0, 1, or 2 copies of the *APOE4* allele. The mean difference between onset and survival was 9.72 years for persons with 2 copies of *APOE4*, 3.1 years for persons with one *APOE4* allele, and 0.6 years in persons without a copy of *APOE4* (Corder et al., 1993). Homozygosity for the *APOE4* allele was virtually sufficient to cause AD by age 80. However, Corder and colleagues (1993) stated that 64 of their 176 autopsy confirmed cases of AD had no copies of *APOE4*, suggesting the existence of other genetic and environmental sources of risk. To summarize AD risk relative to *APOE* genotype, about 40% of all people who develop late-onset AD are carriers of the *APOE4* allele (National Institute on Aging, 2013). Individuals who are heterozygous (1 copy) for the *APOE4* allele are at an increased risk for developing AD and those who are homozygous (2 copies) for the *APOE4* allele are at very high risk for developing AD.

Speculation remains over other risk factors for AD. In a study of thirty same-sex twin pairs, Gatz and colleagues (2010) found that development of incidental dementia was predicted by less favorable lipid values and poorer grip strength. Results from this study also suggest that both Down syndrome (Levernz & Raskind, 1998) and traumatic brain injury (Koponen et al., 2004) are non-modifiable risk factors for AD. Modifiable risk factors may include cardiovascular risk factors and metabolic syndrome (Vanhanen et al., 2006), as well as elevated homocysteine levels (Zhang, Lencz, & Malhotra, 2010). The established relationship among APOE, a lipid transport protein, cardiovascular disease, and AD has led to investigations of

atherosclerosis and hypertension as risk factors for AD (Luchsinger & Mayeux, 2004). Other potential risk factors for AD include inflammation, oxidative stress, and diminished estrogen levels (Aderinwale et al., 2010). Additional genes that may influence the development of late-onset AD include variants of the *SORL1, CLU, PICALM*, and *CR1* genes (National Institute on Aging, 2013). Current study findings based on both candidate gene and genome wide association studies are cataloged on the Alzgene database (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007).

Negative Sequela of Alzheimer Disease (AD).

Symptoms in Alzheimer Disease (AD). While there is a great deal of symptom variability among persons with AD, cognitive and behavioral symptoms are most common and debilitating. The nature and sequela of these symptoms are summarized below.

Cognitive decline. Pathological and progressive cognitive decline is a hallmark finding in AD. Further, substantial variability occurs in the severity and domains of cognitive symptoms in persons with AD throughout the disease trajectory. According to the Centers for Disease Control and Prevention (CDC), cognition is, "a combination of mental processes that includes the ability to learn new things, intuition, judgment, language, and remembering" (Centers for Disease Control and Prevention [CDC], 2011). Cognitive decline has been defined in the literature as "a continuum of cognitive changes; some are considered to be within the spectrum of normal aging, whereas others exceed expected decline and are categorized as mild impairment" (Plassman, Williams, Burke, Holsinger, & Benjamin, 2010, p.182). In a systematic review of the literature, Plassman and colleagues (2010) found that different definitions of cognitive decline made it difficult to make comparisons across studies. The line between normal cognitive decline and

pathological cognitive decline may be unclear due to the inherent subtleties in differentiation between what is "normal," "pathological," and "mildly pathological" from person to person.

Pathological cognitive decline is often referred to as mild cognitive impairment (MCI) or cognitive impairment without dementia when functional impairment is significant but does not warrant a dementia diagnosis (Plassman et al., 2010). Cognitive decline involves worsened performance in one or several cognitive domains such as memory, orientation, language, executive function or praxis, beyond what might be expected for the person's age and educational level (Plassman et al., 2010). People of all ages can experience cognitive decline, which may be caused by stroke, traumatic brain injury, AD and other dementias, or rarely by health issues like medication side effects, vitamin B12 deficiency or depression (CDC, 2011).

The *Diagnostic and Statistical Manual of Mental Disorders, Revised Fourth Edition (DSM-IV-TR)* (2000), produced by the American Psychiatric Association, has limited usefulness with regard to cognitive decline. Several formal diagnoses exist for types of dementia including 'Dementia of the Alzheimer's Type', though it can be difficult to classify cognitive decline into neat diagnostic categories. Imaging tools such as magnetic resonance imaging (MRI) and computed tomography (CT) can detect neurological damage due to atrophy of specific brain areas like the hippocampus or cerebral cortex (Aderinwale et al., 2010; Bird, 2010). More newly developed imaging techniques include single photon emission computerized tomography (SPECT) and positron emission tomography (PET) (Aderinwale et al., 2010). The use of biomarkers for early diagnosis of AD is continually emerging. It is possible that levels of tau phosphorylation and Aβ in cerebral spinal fluid may serve as early indicators of AD (Aderinwale et al., 2010; Bird, 2010). While biomarkers and neuroimaging studies are valuable in the assessment of cognitive decline, they remain expensive and may not always be accessible.

Behavioral symptoms. Behavioral symptoms are a common manifestation of AD. Common behavioral symptoms in AD include sleeplessness, agitation, wandering, anxiety, apathy, anger and depression (Lyketsos et al., 2002; Mega et al., 1996; National Institute on Aging, 2013). These and other personality changes and behavioral symptoms may cause a person to seek an initial clinical evaluation for AD or may emerge over the course of the disease (Petry et al., 1988). Neuropsychiatric symptoms are common and occur in the majority of persons with dementia over the course of the disease (Lyketsos et al., 2002).

Reisberg and colleagues (1987) were some of the early investigators to identify behavioral symptoms in persons with AD. In a chart review of 57 outpatient individuals with AD, 58% of patients demonstrated significant behavioral symptoms. The most commonly identified behavioral symptoms in that sample included delusions, agitation, and sleep disturbance (Reisberg et al., 1987). In 1994, Cummings and colleagues developed the Neuropsychiatric Inventory (NPI) to assess 10 behavioral disturbances commonly occurring in dementia patients, including: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, and aberrant motor activity (Cummings et al., 1994). Shortly thereafter, Mega and others (1996) conducted a foundational study examining the same ten behaviors among persons with dementia. All ten behaviors were significantly more prevalent in persons with AD compared with control subjects (Mega et al., 1996). Apathy emerged as the most common behavior and was exhibited by 72% of persons with AD (Mega et al., 1996).

Agitation and aggression are also common behavioral symptoms in persons with dementia (Cohen-Mansfield, 1996). Neuropsychiatric behaviors may be expressed as physical aggression or striking out, physical agitation such as wandering or picking at things, verbal

aggression or threats, and verbal agitation like repetitive questions or noises (Cohen-Mansfield, 1996). In a publication based on results from the Cardiovascular Health Study, Lyketsos and colleagues (2002) found that 75% of participants with dementia had experienced at least one neuropsychiatric symptom in the past month. The most frequent behavioral disturbances among participants with dementia were apathy, depression, and agitation/aggression, with apathy most frequently displayed (Lyketsos et al., 2002).

Apathy in Alzheimer Disease (AD)

Apathy is a highly prevalent behavioral symptom in persons with AD, occurring in over 90% of persons with AD across the disease trajectory with varying severity (Benoit et al., 2008; Mega et al., 1996). Further, apathy is not typically a transient behavioral symptom, but persists across the illness trajectory with varying severity (Benoit et al., 2008; Mega et al., 1996). While common, apathy is a neuropsychiatric behavior often under-recognized in persons with AD (Landes et al., 2001; Lerner et al., 2007; Mega et al., 1996; Monastero et al., 2006; Robert et al., 2010). Apathy was the most frequently observed neuropsychiatric symptom among persons with dementia in a study of over 600 individuals (Lyketsos et al., 2002). The prevalence of apathy, however, was significantly less than 36%, as reported by Mega and colleagues (1996). In a study of persons with probable AD, authors concluded that patients with apathy suffered from a subtype of AD with greater clinical severity, poorer prognosis, and increased mortality risk (Vilalata-Franch, Calvo-Perxas, Garre-Olmo, Turro-Garriga, & Lopez-Pousa, 2013).

Operational Definition of Apathy

Just as there is a lack of clarity surrounding the conceptual definition of apathy, there is also confusion surrounding the operationalization of apathy. The *DSM-IV-TR* has limited usefulness in defining or clinically identifying apathy. The *DSM-IV-TR* does not presently

recognize apathy as a unique diagnosis, but apathy may receive more attention in the *DSM-5,* according to a presentation at the annual meeting of the American Neuropsychiatric Association (McNamara, 2005).

Apathy is specifically used to describe the following four disorders in the *DSM-IV-TR*: inhalant intoxication, opioid intoxication, apathetic type of personality change due to a general medical condition, and postconcussional disorder (American Psychiatric Association, 2000; McNamara, 2005). Apathy is also included as a symptom for various disorders in the *DSM-IV-TR*. Specifically, apathy is mentioned in association with schizophrenia, delirium, dementia due to Human Immunodeficiency Virus (HIV), dementia due to head trauma, dementia due to Pick's disease, amnestic disorder due to a general medical condition, and separation anxiety disorder (American Psychiatric Association, 2000). Possible symptom synonyms for apathy in the *DSM-IV-TR* include lack of interest, lack of feeling, lack of concern, indifference, flat affect, and emotional unresponsiveness (American Psychiatric Association, 2000).

Neuroimaging tools such as magnetic resonance imaging (MRI) and computed tomography (CT) can detect neurological damage due to atrophy of specific brain areas like the hippocampus or cerebral cortex, which are often implicated in AD (Aderinwale et al., 2010; Bird, 2010). Neuroimaging tools have also been used to better understand apathy (Craig et al., 1996; David et al., 2008; Robert et al., 2006). Craig and colleagues (1996), as well as Robert and colleagues (2006), used single photon emission computed tomography (SPECT) to examine regional cerebral perfusion alterations in relation to the presence and severity of apathy. Correlations between SPECT and apathy as measured by the NPI were the focus for Craig and colleagues (1996), while Robert and colleagues (2006) operationalized apathy as measured by the Apathy Inventory (IA). The presence of apathy was associated with more severe dysfunction

in the prefrontal and anterior temporal areas of the brain based on cerebral perfusion studies (Craig et al., 1996). Robert and colleagues (2006) found correlations between apathy and right frontal and right inferior temporal lobe perfusion. SPECT has also been used to study correlations between apathy and dopamine transporter (DAT) uptake in patients with AD or dementia with Lewy body (DLB) (David et al., 2008), suggesting that persons presenting with apathy due to AD or DLB have some degree of dopaminergic neuronal loss (David et al., 2008).

Skin conductivity or change in posture may also be potentially useful in operationalizing responsiveness and change in arousal. In a study by Hill and colleagues (2010), the level of activity participation was measured using an instrument designed by Kovach & Magliocco (1998). The instrument addressed responsiveness using the following scale: 0 (dozing with eyes closed), 1 (awake but not engaged in the activity), 2 (passive engagement in the activity), and 3 (actively engaged) (Kovach & Magliocco, 1998). Scores were assigned based on videotaped footage of residents engaging in prescribed activities. Researchers established a cut-off time of 20 minutes so that time on task measurements ranged from 0-20 minutes, though protocols related to the decision whether a resident was engaged or disengaged were not specified (Hill et al., 2010). These objective measures of apathy hold promise, but continue to be experimental and costly. Therefore, well-validated clinical evaluations tools, such as the Neuropsychiatric Inventory (NPI) and Apathy Inventory (IA) remain widely used in clinical and research settings at this time (Ishii et al., 2009) and are further discussed in Chapter 4.

Factors Associated with the Presence and Severity of Apathy

Background Factors.

Demographic characteristics. Individual characteristics, such as age, gender and ethnicity may influence symptoms, such as apathy, in persons with AD. To date, data related to

the prevalence of apathy among persons with dementia are not frequently stratified by these demographic characteristics. In a cohort study of 491 persons with AD, however, patients with apathy were mostly men (X^2=8.74, p=0.003) (Vilalata-Franch et al., 2013).

Genetics. Genetics play a role in symptom variability among persons with AD (Monastero et al., 2006; Schutte et al., 2011). Monastero and colleagues (2006) conducted a study examining the association between the *APOE4* genotype and neuropsychiatric symptoms in persons with AD. Apathy was the most common disturbance reported and was present in two-thirds of participants with AD. *APOE4* carriers showed a higher frequency of apathy than non-carriers, suggesting a relationship between the *APOE4* allele and apathy in persons with AD. In a study by Schutte and colleagues (2011), single polymorphisms within the *Saitohin* and *APOE* genes demonstrated association with increased cognitive and functional impairment. The *APOE4* allele was also associated with increased baseline levels of physical agitation in this 12 month repeated measures investigation of symptom variability among institutionalized persons with AD (Schutte et al., 2011).

Oxytocin (OT) is a candidate gene particularly relevant to the study of apathy. OT has been implicated as an important hormone in mother-infant bonding (Douglas, 2010). In addition, OT is implicated as a moderator of human social behaviors with possible significance to social decision-making and quality of bonding behavior (Averbeck, 2010; Campbell, 2010; Douglas, 2010; Ross & Young, 2009). Variations in OT receptor expression have been linked to differences in a mother's sensitivity to her children's behavior (Bakermans-Kranenburg & van Ijzendoorn, 2008) and to maternal behaviors such as licking, grooming, and nursing postures in animal models (Francis, Champagne, & Meaney, 2000). When OT is released from the hypothalamus, it binds to OT receptors, which mediate the effects of OT on multiple target

neurons in the brain (Averbeck, 2010; Campbell, 2010). OT receptors exist throughout body tissues, but are highly concentrated in the amygdala (Huber, Veinante, & Stoop, 2005).

Multiple theories regarding OT exist, but OT may influence social behavior by promoting increased gaze to the eye region of the human face, promoting trust, or serving a role in social memory (Averbeck, 2010; Campbell, 2010). Studies have begun to consider a possible role of pathological OT signaling in psychiatric disorders like schizophrenia (Averbeck, 2010), autism spectrum disorders (Lerer et al., 2008) and Attention Deficit Hyperactivity Disorder (Park et al., 2010). OT may be a biomarker of social distress that accompanies gaps or problems with social relationships dependent on seeking close connections or association with others (Taylor, 2006). This evidence from both human and animal studies provides strong rationale for exploring the extent to which DNA variations within the *Oxytocin Receptor* (*OXTR*) gene influence the presence and severity of apathy in persons with AD.

Lerer and colleagues (2008) undertook a comprehensive study of all 18 tagged SNPs across the *OXTR* gene region, which had been previously identified using HapMap data and the Haploview algorithm. A sample of 152 participants with autism spectrum disorders from 133 families were genotyped and significant associations with single nucleotide polymorphisms (SNP) and haplotypes were observed with autism spectrum disorders (Lerer et al., 2008). A haplotype block composed of five loci (rs237897-rs13316193-rs237889-rs2254298- rs2268494) was significantly associated with autism spectrum disorders ($p=0.009$) and a single haplotype within that block showed an especially significant association ($p=0.00005$) (Lerer et al., 2008). Associations related to IQ, communication and socialization suggest that *OXTR* may shape both cognition and daily living skills (Lerer et al., 2008).

Park and colleagues (2010) investigated whether *OXTR* polymorphisms previously implicated in autism were also associated with Attention Deficit Hyperactivity Disorder (ADHD). An association study of 350 participants with ADHD and their parents failed to produce an association between *OXTR* and the ADHD phenotype. However, there was a significant correlation between social cognitive impairments and a single *OXTR* SNP (rs53576) ($F=5.24$, $p=0.007$) in a subset of 112 ADHD probands (Park et al., 2010). Post-hoc analyses demonstrated that the AA genotype was associated with better social ability in comparison to the AG genotype among probands with ADHD. Significant evidence for CC genotype association with poorer social ability than the TT genotype for SNP rs13316193 ($F=3.09$, $p=0.05$) was also demonstrated in post-hoc analyses (Park et al., 2010). These findings support the relationship between *OXTR* and social behavior. In addition, Park and colleagues (2010) reference evidence for alteration of gene function for the following three *OXTR* SNPs: rs237885, rs13316193 and rs237995.

Cognitive abilities. Cognitive ability is a background factor that may also influence apathy. According to Volicer and colleagues (1999), cognitive dysfunction greatly limits one's ability to engage in independent activities that he/she might have enjoyed before the onset of dementia or AD. However, Orrell and Harmer (2008) found that patients in various stages of dementia were able to participate in meaningful activities. In addition, Algase and colleagues (1996) indicated that the number of NDBs significantly increases with greater cognitive impairment. In a study by Ready and colleagues (2003), behavior change in AD, including apathy, was modestly associated with global cognitive impairment ($r=.025$, $p=0.11$). Behavioral problems were more severe in those with greater cognitive dysfunction. (Ready, Ott, Grace, & Cahn-Wiener, 2003).

Research by Vilalata-French and colleagues (2013) demonstrated a significant correlation between cognitive status and the presence of apathy. Apathy was measured using the NPI-Apathy, while cognition was assessed using the Mini Mental Status Exam (MMSE) and the Cambridge Cognitive Examination (CAMCOG), in a cohort study of 491 individuals. Patients with apathy presented with lower MMSE scores (t=2.241, f=156.143, p=0.026) and CAMCOG scores (t=2.938, df=147.249, p=0.0004). However, cognitive status was not determined to be a risk factor for apathy, based on logistic regression analysis, among the 491 individuals with mild-moderate AD (Vilalata-Franch et al., 2013).

Proximal Factors.

Social environment. Modified environments for persons with dementia were explored as early as the 1980's. Dementia special care units within long-term care facilities have long provided a modified social environment for persons with dementia by including specialized programming, specialized staff, and family involvement (Maas, 1988). Maas and Buckwalter (1990) identified a significant decrease in behavioral symptoms like emotional and physical outbursts, as well as increased resident and staff interactions, among the special care unit experimental group in their intervention study (Maas & Buckwalter, 1990). Work by Yao and Algase (2006) also supports the positive impact of a supportive social environment on resident behaviors. Volicer and colleagues (1999) recognize that activities must be, "tailored to the remaining strengths and abilities of the individual, and take into consideration life history, premorbid likes and dislikes, and present preferences" (p. 91). Further investigation of environmental and social stimulation specifically oriented to an individual's own interests, accomplished by altering the social environment as a treatment for apathy, has also been suggested (Robert et al., 2010). To that end, Hill and colleagues (2010) had success in tailoring

activities to individual functional abilities and personality preferences in order to improve both the time and level of participation in their intervention targeting activity engagement among nursing home residents with dementia.

Function. The relationship between apathy and functional status is poorly understood. This lack of understanding is at least partly attributable to a lack of conceptual clarity surrounding apathy and functional health outcomes. In a seminal article by Katz and colleagues (1963), investigators developed a measure to evaluate the natural changes of function among ill and well older adults in order to assess the need for care in community facilities, rehabilitation centers, nursing homes, and home care programs (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963). Katz and colleagues (1963) suggested with good evidence that older adults lose functional ability in a pattern similar to the gain of function in early development. It is interesting to consider how apathy might fit into this discussion of functional ability. For example, when considering function in persons with AD and apathy, one must consider whether an individual is *able* to perform a given task, *does perform* a given task, or whether the individual is able to perform a given task and does so *with prompting* and stepwise directions. Additionally, in what order are these functional skills lost in persons with apathy and AD?

According to Gomar, Harvey, Bobes-Bascaran, Davies, and Goldberg (2011), everyday function refers to "the self-initiated ability to perform those basic and complex behaviors necessary to live independently in the community" (p. 916). Important in this definition is the use of "self-initiated ability" as a qualifier for function. Authors developed and validated a short form version of the University of California, San Diego, Performance-based Skills Assessment (UPSA). The UPSA short form was found to be a rapid and reliable measure of functional capacity able to detect performance impairment and to discriminate among healthy subjects,

individuals with mild cognitive impairment (MCI), and patients with AD (Gomar, Harvey, Bobes-Bascaran, Davies, & Goldberg, 2011).

Kaplan and Foldi (2009) presented a review considering three perspectives used to classify activities of daily living (ADL) including: tasks categorized by their *environment*, tasks defined by *performer skill*, and a *resource-based perspective* that integrates environment and performer conditions. Authors proposed that patterns of functional decline occurring in early AD are shaped by impairments of attention (Gomar et al., 2011). Attentional functions may be one mediator of the decline in functional ability in AD (Kaplan & Foldi, 2009).

Several studies addressed both apathy and depression in relationship to functional status or disability (Benoit et al., 2008; Lam et al., 2008). Benoit and colleagues (2008) examined the relationship between apathy and depression in a large sample of community dwelling elderly adults with AD. Inclusion criteria were based on a diagnosis of possible or probable AD. The team evaluated clinical, functional, and therapeutic variables in relationship to apathy and/or depression. Findings indicated that apathy, as a separate construct from depression, is highly prevalent in mild to moderate stages of AD (Benoit et al., 2008). Additionally, apathy is related to functional outcomes in AD, independent from cognitive status. An apathy prevalence of 43% in the sample and was associated with more pronounced deficits in global cognition and everyday life and instrumental abilities, compromised nutritional status, and caregiver burden (Benoit et al., 2008). Apathy was measured using the apathy subscale of the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994). Authors calculated a frequency per severity score and considered that apathy was clinically significant whenever its score was superior to 3 (Benoit et al., 2008). Functional outcomes were evaluated using the Inventory for Activities of Daily Living (IADL) (Lawton, 1969). Similarly, Verhey, Aalten, and De Vugt (2003) regarded NPI domain

scores of 4 or more as clinically significant in their study of persons with dementia and reported apathy as the most commonly experienced symptom, with a prevalence of 40.2% (Verhey, Aalten, & De Vught, 2003).

While the relationship between apathy and functional status is poorly understood, there is supporting literature for the deleterious effect of apathy on functional status in persons with dementia (Bouwens et al., 2008; Lam et al., 2008). Lam and colleagues (2008) examined the relationships between apathy, depression, and functional impairment in Chinese persons with questionable dementia or mild AD. Apathy and depression were rated using the NPI, while functional disability was measured using the Disability Assessment for Dementia (DAD). Interestingly, both severity of apathy and depression symptoms were associated with poorer functional performance in questionable dementia, while apathy alone was associated with poorer functional performance among those with AD (Lam et al., 2008). Persons with questionable dementia and apathy, depression, or the coexistence of apathy and depression had poorer functional performance than those with neither apathy nor depression. The coexistence of apathy and depression was not associated with more severe functional disability than either symptom alone. In persons with AD, those with apathy had poorer functional outcomes than those without apathy and AD. To that end, depression without apathy was not associated with more severe functional disability (Lam et al., 2008). In summary, Lam and colleagues (2008) suggest that apathy and depression may be associated with the degenerative process of dementia as a consequence of progressive cognitive decline or as moderating variables. Additionally, when dementia becomes clinically apparent, apathy, unlike depression, contributes to a motivational loss in functioning (Lam et al., 2008).

Bouwens and colleagues (2008) discovered that among patients with AD, cognitive and global severity measures were moderately associated with process scores on the Assessment of Motor and Process Skills. While not their major finding, Bouwens and colleagues (2008) concluded that the presence of apathy was the only NPI item that, in combination with Mini-Mental State Examination (MMSE) scores and the cognitive component of the revised Cambridge Examination for Mental Disorders of the Elderly scores, contributed significantly to the variance in Assessment of Motor and Process score (Bouwens et al., 2008).

Much of the apathy literature is immersed within published work discussing frontal lobe deficits or frontally mediated behavioral disturbance (Boyle et al., 2003; Norton, Malloy, & Salloway, 2001; Ready et al., 2003). Research by Boyle and colleagues (2003) demonstrated that frontally mediated behavioral disturbances, such as apathy, were associated with functional impairment in mild to moderate AD. Specifically, multiple-regression analyses revealed that executive cognitive dysfunction and apathy scores accounted for 44% of the variance in instrumental activities of daily living (IADL). Executive cognitive dysfunction alone accounted for an additional 17% of the variance, and apathy scores alone explained 27% of the variance in IADL (Boyle et al., 2003). Based on these results, Boyle and colleagues suggested the prediction of functional impairment in mild to moderate AD based on executive dysfunction and the presence of apathy (Boyle et al., 2003).

Work by Norton and colleagues (2001) demonstrated a strong relationship between the presence of behavioral disturbances in dementia and poor performance of both activities of daily living (ADL) and IADL. Data indicated that of the three frontal-lobe behaviors measured by the Frontal Lobe Personality Scale (FLOPS), apathy most strongly predicted failure of both ADL

and IADL. The Apathy subscale of the NPI was also used and correlated with failure in ADL, but was less strongly associated (Norton et al., 2001).

The relationship between apathy, cognition, and function has also been examined in the context of mild cognitive impairment (MCI). MCI has been classified as likely to progress to more severe dementia or AD. In a study of apathy and executive dysfunction in mild cognitive impairment and AD, Ready and colleagues (2003) found that changes in frontally mediated behaviors are common in early cognitive impairment and MCI. Specifically, these changes in frontally mediated behaviors, including apathy, are present even before a change in functional decline is evident (Ready et al., 2003). Among persons with MCI and AD, statistically significant difference scores compared with premorbid ratings in apathy were reported. Between groups differences in apathy were not significant (Ready et al., 2003).

While there is much evidence supporting a significant relationship between apathy and functional health status, some researchers have drawn contrary conclusions. For example, Yu, Kolansowski, and Litaker (2006) examined the association of physical function with two behavioral symptoms, agitation and passivity, in nursing home residents with dementia. Despite high levels of passivity among sampled individuals, it was found that physical function was not related to passivity in that study (Yu, Kolanowski, & Litaker, 2006). Authors suggested that efforts to improve physical function may have the greatest impact on behaviors in early stages of dementia, but acknowledged that a small sample size may have prevented a significant association between physical function and passivity (Yu et al., 2006).

Nonpharmacologic Interventions for Reducing Apathy in Persons with Dementia

The development and testing of nonpharmacologic interventions to reduce apathy in persons with AD is an important avenue for nursing research. Several different types of

interventions have been evaluated. For example, Dykstra Goris (manuscript in development) performed an integrated literature review including fifteen studies focused on nonpharmacologic interventions for reducing apathy in persons with dementia. Nonpharmacologic interventions for reducing apathy varied widely in approach. Several interventions included music alone or in combination with other activities (Ferrero-Arias et al., 2011; Fischer-Terworth & Probst, 2011; Holmes, Knights, Dean, Hodkinson, & Hopkins, 2006; Raglio et al., 2010; Raglio et al., 2008). Hattori and colleagues (2011) used art therapy as a form of intervention to reduce apathy, while Jarrott and Gigliotti (2010) utilized twice-weekly horticultural based programming (Hattori, Hattori, Hokao, Mizushima, & Mase, 2011; Jarrott & Gigliotti, 2010).

Other investigators took a more cognitive approach by utilizing cognitive stimulation therapy (Niu, Tan, Guan, Zhang, & Wang, 2010) or a standardized kit-based activity (Politis et al., 2004). Multisensory stimulation techniques were also employed in an attempt to reduce apathy among persons with dementia in the form of Multi-sensory Behavior Therapy (Staal et al., 2007) or *Snoezelen*-based care (van Weert, van Dulmen, Spreeuwenberg, Ribbe, & Bensing, 2005). *Snoezelen*-based care is a form of multi-sensory stimulation used to stimulate primary senses of sight, hearing, touch, taste and smell using various lighting effects, tactile surfaces, music and essential oils, among persons with dementia and other cognitive deficits (Chung, Lai, Chung, & French, 2002; Pinkney, 1997). Some research teams focused less on the type of intervention, and more on tailoring interventions to the participant's skill level or personality (Kolanowski et al., 2005; Kolanowski et al., 2011; Lam et al., 2010). Finally, Tappen and Williams (2009) intervened with therapeutic conversation (Tappen & Williams, 2009). Select interventions demonstrated effectiveness, but lacked long-term follow-up.

Overall, a limited number of interventions have been tested and impact on apathy has been modest. These results may be, in part, related to an incomplete understanding of the risk factors for apathy. Risk factors for apathy are potential targets for intervention or potential mechanisms for targeting persons with AD at highest risk for apathy. In thinking about risk factors for apathy, genotype data must also be explored. This gap in knowledge prevents healthcare providers from properly identifying which individuals might be more prone to apathy, and identifying how resident characteristics and social environmental factors impact the presence and severity of apathy in persons with AD as well as subsequent functional outcomes. Therefore, a critical need exists to further examine apathy in persons with AD.

The dissertation project addressed this knowledge gap in part, by exploring resident characteristics and social environment factors as predictors of the presence and severity of apathy among persons with AD as a foundation for future intervention research. *OXTR* was also examined as an important potential modifier in the prediction of apathy in persons with AD. The effect of apathy on functional status among this sample was also investigated, as supporting evidence exists for the deleterious effect of apathy on functional status in persons with dementia (Lam et al., 2008)

CHAPTER 4: METHODS/APPROACH

Study Design

This dissertation study employed a cross-sectional correlational descriptive design to examine the extent to which individual and social environmental factors influence the presence and severity of apathy in persons with Alzheimer Disease (AD) by addressing the following specific aims: 1) Examine the extent to which individual characteristics (demographics and cognitive status) and social environment factors predict the severity of apathy in persons with AD, after adjusting for AD severity and *Apolipoprotein E-4 (APOE4)* status, 2) Examine the extent to which variations in the *Oxytocin Receptor (OXTR)* gene are associated with apathy in persons with AD, and 3) Examine the extent to which severity of apathy influences functional status in persons with AD, after adjusting for AD severity. This was part of a parent study of gene-environment interactions in the symptoms of AD, in which persons with a diagnosis of possible or probable AD were recruited from long-term care facilities by way of convenience sampling.

Sample and Setting

A sample of community dwelling and institutionalized persons with AD were recruited as part of a parent study in the midwestern United States to examine gene-environment interactions and clinical symptoms in AD (Schutte et al., 2003; Schutte et al., 2011). For this dissertation study, the sample consisted of data previously collected and unanalyzed, as well as data from persons recently recruited as part of the parent study. Participating facilities were identified by convenience to the parent study. Eligible residents within the facilities were recruited via convenience sampling, though all eligible participants had the opportunity to participate, resulting in data available for 66 participants. According to calculations using the Soper online

power calculator tools, a sample of 66 participants yields 80% power to detect a moderate effect size (0.215) with an alpha level of 0.05 and 5 predictor variables (Soper, 2012).

Inclusion Criteria. Inclusion criteria for participants in this dissertation study included: 1) persons over the age of 21 years, 2) English-speaking, and 3) with a diagnosis of possible or probable AD based on criteria by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer Disease and Related Disorders Association (ADRDA) criteria (McKhann et al., 1984). This information was ascertained from participants' legal representatives or upon chart review.

Exclusion Criteria. Participants with a comorbid diagnosis of a major psychiatric disorder, including major depression, schizophrenia, or bipolar disease, were excluded from this dissertation study.

Instrumentation: Background Factors

Demographic Characteristics. General data related to demographic characteristics were collected via chart review and included age, gender, ethnicity and level of education. Demographic data related to cognitive abilities were also collected from participants' legal representatives or upon chart review and included: age of first onset of dementia symptoms, years since symptom onset, and whether a physician or other practitioner made a formal diagnosis of AD.

Genotype/Genetic Measurement. Genomic deoxyribonucleic acid (DNA) were extracted from either saliva or blood samples for genotyping of five *OXTR* gene variants (rs2268491, rs6770632, rs237885, rs53576, rs237895) and the common allelic variants of the *APOE* gene (rs429358, rs7412). Please see the Data Collection Procedures and single nucleotide

polymorphism (SNP) Identification and Testing sections of this chapter for specific genotyping methods and details regarding SNP selection.

Cognitive Abilities.

Severe Impairment Battery (SIB). The Severe Impairment Battery (SIB) served as the primary measure of cognition for the dissertation study and was collected as part of the parent study. The SIB was originally developed for research, in order to evaluate patients with severe dementia not well assessed with conventional neuropsychological testing like the Mini-Mental State Examination (MMSE) (*Contemporary approaches to neuropsychological assessment*, 1997; Panisset, Roudier, Saxton, & Boller, 1994). The tool assesses multiple domains of cognition including: social interaction, memory, orientation, language, attention, praxis, visuospatial ability, construction and orientation, using verbal single-step commands and verbal or gestural cues (Panisset et al., 1994). The SIB is a 40-item measure of cognition, with possible scores ranging from 0 to 100. A score of 100 indicates no cognitive impairment, while a score of 0 indicates severe cognitive impairment (Panisset et al., 1994). Complete point values are awarded for correct responses, but partial point values are awarded for nonverbal and partially correct responses. In work by Panisset and colleagues (1994), convergent validity with the MMSE was determined at $r=0.77$ ($p<.001$). Convergent validity with the Mattis Dementia Rating Scale was also determined at $r=0.77$ ($p<.001$). Inter-rater reliability for the SIB was $r=0.89$ - 0.99 ($p<.0001$), and test-retest reliability after two weeks was reported at $r=0.85$ ($p<.001$) (Panisset et al., 1994).

Goldstein and Incagnoli (1997) suggest that the SIB has the most sensitivity in subjects with the most significant cognitive impairment, but that it is best suited for patients that can be described as *moderately severely impaired*, rather than *severely severely impaired*. They suggest

that there is not a floor effect when the SIB is used with severely impaired participants. In practice, the investigator has determined that the SIB may be vulnerable to floor effects in longitudinal studies if participants score very low (i. e. five points) during the initial assessment. There is the little room to evaluate further decline in what Goldstein and Incagnoli (1997) call *severely severely impaired* patients. However, the literature states that floor effects are less of a problem with the SIB than with other tools like the MMSE (Folstein, Folstein, & McHugh, 1975), Dementia rating scale of Mattis (1976), and Functional Assessment Staging of Dementia (Reisberg, Ferris, & Franssen, 1985). Ceiling effects are of little consequence with regard to the SIB due to the progressive nature of cognitive decline and AD. The SIB is available in English, Spanish, French, and Italian, and strong reliability and validity coefficients have been replicated for each of these ethnolinguistic groups (*Contemporary approaches to neuropsychological assessment*, 1997).

Instrumentation: Proximal Factors

Social Environment.

Categorical variable. A categorical variable for social environment, based on participant residence at time of data collection, served as the primary measure of social environment for this dissertation project. Categories to classify social environment as measured by residence at time of data collection included: 1) own home, 2) family member's home, 3) assisted living/adult foster care, 4) assisted living/adult foster care with dementia-specific care unit, 5) extended care facility (ECF)/long term care (LTC) facility/nursing home, 6) ECF/LTC facility/nursing home with dementia-specific care unit, and 9) other. Social environment information was collected as part of the demographic questionnaire.

Following data collection and in order to facilitate data analyses, categories were collapsed into two groups: dementia-specific environment and non dementia-specific environment. The collapsed dementia-specific environment group encompassed individuals dwelling in their own home, a family member's home, assisted living/adult foster care with dementia-specific care unit, or an ECF/LTC facility/nursing home with a dementia-specific care unit. The remaining categories were collapsed to form the non-dementia-specific environment group. Because an individual's own home or a family member's home is more individually tailored and familiar, more like a dementia-specific care unit, the own home and family member's home categories were included within the dementia-specific environment group in an effort to capture characteristics of the social environment.

Ambiance Scale (AS). The Ambiance Scale (AS) served as a secondary measure of social environment for this dissertation project, as data were available for only a subset of the sample (n=23). Algase and colleagues developed the AS to operationalize the concept of social environment as included in the NDB model (Algase et al., 1996; Algase et al., 2007). The original instrument (Struble, 1995) was modified with an interest in the effects of environments on the affect and behavior of persons with dementia (Algase et al., 2007). The AS is intended for use by observers in rating the immediate and visually accessible environment for selected characteristics related to emotional valence (Algase et al., 2007). However, it does not evaluate behavior going on in the environment or evaluate emotions elicited by the environment. The instrument includes thirteen adjective pairs, which are formatted using a revised semantic differential scaling model (+2 to -2), resulting in a possible scoring range from -26 to +26 (Algase et al., 2007). To facilitate interpretation, scores were summed and transformed to values 0 to 1. Values closer to zero denote more embellished, stimulating, unpretentious, colorful,

warm, peaceful, welcoming, informal and novel spaces. In contrast, a value of 1 represents a living space that is stark, custodial, pretentious, drab, cold, chaotic, impersonal, formal and boring. The overall AS has demonstrated strong reliability (Cronbach's alpha 0.89-0.91) (Algase et al., 2007). Importantly, the AS also differentiates between facility types (nursing home vs. assisted living) and room types (shared spaces vs. private spaces).

Instrumentation: Need Driven Behaviors (NDB)

Apathy.

Neuropsychiatric Inventory-Nursing Home (NPI-NH). The apathy subscale of the NPI-NH served as the primary measure of apathy for this dissertation study and was collected as part of the parent study. The Neuropsychiatric Inventory (NPI) is a clinical instrument for evaluating behavioral disturbances in persons with dementia (Cummings et al., 1994; Kaufer et al., 2000). The tool measures apathy, is credited with excellent reliability and validity, and is widely used (Cummings et al., 1994; Kaufer et al., 2000; Lerner et al., 2007). The original NPI was designed to evaluate patient behavior since the onset of dementia; specifically, whether a given neuropsychiatric behavior has been present over the past month. If the caregiver indicates that a behavior is present, the domain is further explored with 7 or 8 sub-questions in order to confirm the presence of the behavior (Cummings et al., 1994). Apathy is operationalized with questions related to patient loss of interest in the surrounding environment, decreased likelihood to initiate conversation, lacking emotions, loss of interest in friends or family, decreased enthusiasm about interests, and withdrawn affect. The caregiver is then asked to rate the severity (1=mild, 2=moderate, 3=severe) and frequency (1=occasionally, less than once per week; 2=often, about once per week; 3=frequently, several times per week but less than every day; 4=very frequently,

once or more per day or continuously) of the behavior (Cummings et al., 1994). Frequency and severity scores are then multiplied to create a maximum score of 12 for the apathy domain.

At the time of development, a panel of nationally and internationally known experts in geriatric psychiatry, behavioral neurology, and neuropsychology established content validity of the NPI (Cummings et al., 1994). Overall reliability of the NPI was reported as Cronbach's alpha 0.88 (Cummings et al., 1994). Test-retest reliability, with a time interval of three weeks, was reported as 0.79 for the frequency score ($p=.0001$) and 0.86 for the severity score ($p=.0001$) (Cummings et al. 1994). Cummings and colleagues (1994) did not establish cutoff scores for each of the subscales, nor determine a score on the apathy subscale that might indicate clinically meaningful apathy.

Wood and colleagues (2000) developed and assessed the validity of the nursing home version of the NPI (NPI-NH), which was used in this dissertation study. In the NPI-NH, nursing staff members replace family caregivers as informants (Wood et al., 2000). The NPI-NH demonstrates inter-rater reliability at 0.283-0.914 ($p<.05$) and concurrent validity with the Cohen-Mansfield Agitation Inventory (CMAI) at $r=0.52$ ($p<.0001$) (Wood et al., 2000).

Apathy Inventory (IA). The Apathy Inventory (IA) served as a secondary measure of apathy in this dissertation study, due to its inclusion of the emotional, behavioral, and cognitive aspects of apathy. The IA was more recently incorporated as part of the parent study and data were available for the most recently recruited subset of the sample ($n=22$). The IA was designed to provide an assessment of emotional, behavioral, and cognitive aspects of apathy in patients with brain disorders such as AD, Parkinson's disease, and mild cognitive impairment, and consists of two sets of questionnaires (Robert et al., 2002). One set of questionnaires may be used to obtain information from a spouse or caregiver intimately familiar with the patient's

behavior, and the second to directly evaluate the patient (Robert et al., 2002). These are referred to as IA Caregiver and IA Patient, respectively, and may be used individually or in tandem. The IA Caregiver was utilized as part of this dissertation study.

The IA Caregiver is best administered in the absence of the person with dementia and is formatted after the NPI (Robert et al., 2002). Robert and colleagues (2002) note that questions are to be asked in an interview format, exactly as written. Behavioral traits that have been present throughout life, even if abnormal, are not to be taken into account in the IA assessment (Robert et al., 2002). The IA Caregiver includes three subscales, one each relating to emotional blunting, lack of initiative, and lack of interest. For each of the three subscales, the maximum score is 12 (Frequency 1-4 x Severity 1-3), providing an IA Caregiver maximum total score of 36 (Robert et al., 2002).

Concurrent validity for the IA Caregiver was determined by comparing the IA individual item and global scores with the apathy subscale of the NPI (Robert et al., 2002). Lack of initiative and the lack of interest questions, pertaining to the behavioral and cognitive domains of apathy, were significantly correlated with the NPI Apathy subscale ($r=0.22$-0.66; $p<.05$-$p<0.001$). The overall reliability for the IA Caregiver was reported as Cronbach's alpha 0.84 (Robert et al., 2002). Inter-rater reliability was reported as very high (Kappa=0.99) for all item scores and the global score. Test-retest reliability was reported as: Emotional Blunting subscale (Kappa=0.99), Lack of Initiative subscale (Kappa=0.97), Lack of Interest subscale (Kappa=0.99), and global score (Kappa=0.96) (Robert et al., 2002). The time interval between assessments was not reported, but Robert and colleagues (2002) note that the IA may be used as a one-time assessment or to evaluate changes over time. Constructs and Psychometrics of the IA and NPI-NH are detailed in Table 1.

Table 1. Comparison of the Constructs and Psychometrics of the IA and NPI-NH

Instrument	Constructs	Validity	Reliability
Neuropsychiatric Inventory – Nursing Home Version (NPI-NH) *Primary measure of apathy* Based on the original NPI by Cummings et al. (1994).	Delusions; Hallucinations; Agitation; Depression; Anxiety; Elation; **Apathy**; Disinhibition; Irritability; Aberrant Motor Behavior; Sleep Disturbance; Appetite	Concurrent validity between the apathy subscale of the NPI (NPI-Apathy) and the Apathy Evaluation Scale (AES) has been established as statistically significant, but not very high (Clarke et al., 2007).	Overall reliability of the NPI was reported as Cronbach's alpha 0.88 (Cummings et al., 1994). The NPI-NH demonstrated inter-rater reliability at 0.283-0.914 ($p<.05$) (Wood et al., 2000). Test-retest reliability (3 weeks) was reported as 0.79 for the frequency score ($p=.0001$) and 0.86 for the severity score ($p=.0001$) (Cummings et al. 1994).
Apathy Inventory (IA) *Secondary measure of apathy*	**Emotional** (emotional blunting or lack of emotional responses), **Behavioral** (lack of initiative or diminished goal-directed behavior), and **Cognitive** (lack of interest or diminished goal-directed cognition) **aspects of apathy** (Robert et al., 2002).	IA Caregiver behavioral and cognitive domains of apathy demonstrated concurrent validity with NPI apathy subscale ($p<0.001$) (Robert et al., 2002).	Overall reliability for the IA Caregiver was reported as Cronbach alpha 0.84 (Robert et al., 2002). Inter-rater reliability for the IA Caregiver was reported as very high (Kappa=0.99) for all item scores and the global score (Robert et al., 2002). Test-retest reliability for the IA Caregiver was reported as: emotional blunting (Kappa=0.99), lack of initiative (Kappa=0.97), lack of interest (Kappa=0.99), and global score (Kappa=0.96) (Robert et al., 2002).

Instrumentation: Function

Functional Abilities Checklist (FAC). The Functional Abilities Checklist (FAC) served as the primary measure of functional ability for the dissertation work and was collected as part of the parent study. The FAC is a 28-item tool including four domains of function assessed with four subscales: Self Care ability, Inappropriate Behaviors, Cognitive Status, and Agitated Behavior (Maas & Buckwalter, 1990). The instrument is scored based upon the assessment of participant behaviors observed during the previous week, with ratings on a scale from 1 to 4 (1=never, 4=multiple times per day). Higher scores indicate a higher degree of functional impairment (Maas & Buckwalter, 1990). Reliability for the total scale has been reported as Cronbach's alpha 0.85 (n=142) with the following reliability values for the FAC subscales: Self Care (0.85), Inappropriate Behavior (0.84), Cognitive Status (0.74) and Agitated Behaviors (0.72) (D. A. Reed, personal communication, April 4, 2013). Additionally, pilot work among a sample of institutionalized persons with AD provided an intra-class correlation of 0.76 for the FAC (Schutte, 2013). For this dissertation study, data were analyzed by calculating a mean total score for each of the four subscales as advised by FAC authors (D. A. Reed, personal communication, April 4, 2013).

Functional Assessment Staging of Alzheimer Disease (FAST). The FAST served as the secondary measure of functional ability and was collected as part of the parent study. The FAST expands on the Global Deterioration Scale (GDS) to provide a global measure of functional decline in persons with severe AD by classifying individuals according to seven major functional levels (Reisberg et al., 1985). FAST stages 1 to 5 correspond to the global levels of cognition and functional ability as measured by the GDS, but further expands upon levels 6 and 7 to include more detailed functional status indicators appropriate for persons with AD. The

lowest functional level of each participant must be indicated; with higher scale scores indicating more severely compromised functional status (Reisberg et al., 1987; Reisberg et al., 1985). Pilot work among a sample of institutionalized persons with AD provided an intra-class correlation of 0.88 for the FAST (Schutte, 2013).

Procedures

Recruitment Procedures. Participants were recruited from both the community and long-term care facilities located in the midwestern United States as part of the parent study, utilizing a consent procedure including evaluation of participant capacity to consent. Facility staff at the long-term care facilities identified potential participants with possible or probable AD. Facility staff then sought permission for the investigators to contact the legal representative. The research team contacted persons who agreed to receive further study information and provided additional information, clarified questions, and extended the invitation to participate. In most cases, potential participants demonstrated a lack of capacity to consent in which case informed consent was obtained from the legal representative for the individual with AD. Assent forms for the person with AD were also utilized if the investigator determined that the participant demonstrated study understanding and had the ability to provide a written signature.

Data Collection Procedures. Following consent, members of the research team reviewed the medical record in order to collect health history, medical diagnoses, and dementia evaluation data (See Table 2). The investigator contacted the legal representative by phone in order to confirm findings and to seek any additional information on family health history and diagnostic evaluation for AD. In only a few rare cases of discrepancy, the medical record data took priority over that provided by the participant's legal representative. In many cases, legal representatives requested that the investigator refer to participants' charts for confirmation of any

information provided. When facility staff provided information in the form of caregiver interviews, an effort was made to gather the richest data possible. Facility staff members who spent the most time caring for a participant were able to provide the most complete and accurate data and responded to participant-specific questions.

The research team, including the investigator, in each facility completed data collection for the participants with AD. Extensive training, including inter-rater reliability, was completed as part of the parent project (Schutte et al., 2003; Schutte et al., 2011); dual assessments were made on all measures for new data collectors for the first 3 to 5 participants. Discrepancies in scoring were discussed and resolved through consensus, and inter-rater reliability was confirmed. As part of the parent project, booster- training sessions were held periodically. The investigator collected data using all resident assessment measures and completed training through the use of instrument training manuals and one-on-one instruction. Instruments included in this dissertation research were administered at one time point coinciding with baseline or follow-up data collection intervals as determined by the parent study. Data collection procedures included a telephone interview with the legal representative, medical record review, direct resident observation, and facility staff interviews.

Data collection also included obtaining a whole blood sample by phlebotomy or saliva sample by cheek swab as a DNA source. Whole blood samples were either collected by a member of the research team or obtained by a trained phlebotomist via a contracted service within each facility. In the case that peripheral phlebotomy was contraindicated or determined to be too disruptive for the person with AD, a saliva sample was obtained. In some cases, a saliva sample was obtained in lieu of a whole blood sample per family request. Both blood and saliva samples provided high quality DNA. Following DNA extraction, DNA concentration was

measured for each sample, assuring the use of nearly equivalent amounts of DNA for genotyping procedures.

Table 2. Data Collection Summary

Instrument	**# of Items**	**Time Required**	**Data Source**	**Method**
Demographic Characteristics	10	5-10 minutes	Medical record	Chart review
Severe Impairment Battery (SIB)	39	10-30 minutes	Participant with AD	Participant interview
Ambiance Scale (AS)	13	5-10 minutes	Participant room environment	Direct observation of environment
Neuropsychiatric Inventory-Nursing Home (NPI-NH)	60	10-15 minutes	Facility staff	Caregiver interview
Apathy Inventory (IA)	3	5-10 minutes	Facility staff	Caregiver interview
Functional Abilities Checklist (FAC)	28	5-10 minutes	Facility staff	Paper-pencil questionnaire, completed by Caregiver
Functional Assessment Staging of Alzheimer Disease (FAST)	1	5 minutes	Participant with AD	Participant interview & chart review
Laboratory specimen for DNA extraction	1	10-15 minutes	Participant with AD	Phlebotomy or saliva sample collection

Sample processing and genotyping procedures. Whole blood or saliva samples were collected at each site and transported to the D. Schutte laboratory. Blood was stored in a biohazard-labeled cooler for transport. Saliva samples were stable at room temperature until processed. However, blood samples were kept at 4°C, and then processed within seven days of

collection to isolate and store DNA using Puregene DNA Isolation Kits (Qiagen, Valencia, CA). Saliva samples were collected, batched at room temperature, and processed using the Oragene DNA kits (DNAGenotek, Ontario, Canada). The research team had excellent success in extracting consistently high quantities (average 35ug DNA/1ml whole blood; average 35-40ug DNA/1ml saliva) and high quality DNA in using these protocols. DNA from blood and saliva worked equally well in the subsequent genotyping approaches.

The Taqman® quantitative PCR (Applied Biosystems) platform was the primary molecular method used for allele discrimination in the five *OXTR* variants, as well as the *APOE* genotypes. The Taqman® assays used allele-specific PCR amplification to detect single nucleotide polymorphisms (SNPs) in candidate genes. A SNP is a DNA sequence variation, commonly occurring among humans, in which a single nucleotide – A, T, C, G – differs at a particular locus within the genome (Strachan & Read, 2011). On average, a SNP occurs once every 300 basepairs throughout the human genome. These DNA sequence variations can serve as useful biomarkers for exploring the relationship between a candidate gene and phenotype.

The Taqman® system uses two short, invariant primers to amplify the target DNA that is then interrogated with two allele-specific (SNP-specific) probes. These allele-specific probes consist of a fluorescent tag at one end, the specific nucleotide sequence difference midprobe, and a quenching dye at the other end. When the allele-specific probe matches the polymorphic sequence, the probe binds tightly to the DNA, the quencher is cleaved by the 5'exonuclease activity of Taq polymerase, and the reporter subsequently fluoresces. One reporter is released in homozygous samples; both reporters are released in heterozygous samples. The resulting gradient of fluorescence for each of the study samples was read by an automatic sequence-detection system (Applied Biosystems) in the Michigan State University (MSU) Genomics Core

Facility. Assays were run in duplicate and all assays yielded genotype frequencies that were consistent with those expected by Hardy-Weinberg Equilibrium (HWE), a standard quality control step when examining genotype data.

SNP identification and testing. Criteria for identifying SNPs within the *OXTR* gene included: 1) SNPs with empiric evidence for an association with apathy or related phenotypes (Lerer et al., 2008; Park et al., 2010), 2) SNPs known to alter gene function (Park et al., 2010), and 3) SNPs with a minor allele frequency >0.2 (Kent et al., 2002) (see Table 3).

Table 3. Specific Aim 2 SNP Selection

Gene Acronym Locus	SNP rs#	Alleles	MAF
*APOE** 19q	rs429358 rs7412	C/T C/T	0.150 (C) 0.074 (T)
OXTR1 3p26.2	rs237885	G/T	0.469 (T)
OXTR2	rs53576	A/G	0.289 (A)
OXTR3	rs237895	C/T	0.403 (T)
OXTR4	rs6770632	A/C	0.243 (A)
OXTR5	rs2268491	C/T	0.218 (T)
*The *APOE-4* genotype is derived from the 2 SNPs described above. MAF= Minor Allele Frequency (the frequency of the less common allele in a given population).			

Data Analysis

General Data Analysis Strategies. Paper copies of all previously collected questionnaires in the parent study were reviewed and data entered into a new SPSS Statistics software, Version 21.0 (SPSS, Inc., Chicago, IL), file to build the data set for this study. In order to confirm accurate data entry for each participant, double data entry and verification were completed. The investigator double-entered 15% of the data, with cases randomly selected by

row number using an online random number generator. Comparison of original and double-entered data for the randomly selected cases yielded 99.99% accuracy in data entry. Data analysis for the dissertation study was completed using SPSS Statistics software, Version 21.0 (SPSS, Inc., Chicago, IL).

Summary statistics were calculated in order to provide a sample description and to test for relevant assumptions. Descriptive and comparative statistics were utilized to assess the characteristics of the sample, to compare key variables by gender, as well as to compare participants with and without apathy. Missing data were limited to less than 5% the majority of variables, and missing values were considered to be missing at random. Therefore, analyses proceeded without case elimination or imputation of missing data, as advised by the statistical consultant on the dissertation project. Access to data was limited to research team members and hard copy data were stored in a locked file cabinet in a locked research project space. Electronic data were stored on a password-protected computer in a locked office and backed up on the password-protected MSU project drive. See Appendices for further detail concerning protection of human subjects.

Data Analysis Strategies by Specific Aims.

Aim 1. Examine the extent to which individual characteristics (demographics and cognitive status) and social environment factors predict the severity of apathy in persons with AD, after adjusting for AD severity (based on FAST scale score) and APOE4 status. Bivariate relationships were examined between independent and dependent variables (using either ANOVA or Pearson's correlation) in order to identify variables to be included in the regression analyses. Logistic regression analyses were used to determine the relationship between resident and social environmental factors in persons with and without apathy. The specific independent

variables included in these analyses were demographic characteristics (age, gender), cognitive abilities (as determined by total SIB score), and social environment as determined by place of residence (dichotomized as dementia-specific vs. non dementia-specific). Analyses began with hierarchical regression analyses, first adding background factor variables, followed by proximal factor variables. The primary outcome variable for these analyses was presence or absence of apathy as determined by NPI-Apathy subscale score. Multiple regression analyses were also conducted to examine the relationship between these independent variables and severity of apathy (NPI-Apathy frequency x severity score as continuous level data), using the same hierarchical strategy.

Aim 2. Examine the extent to which variations in the Oxytocin Receptor (OXTR) gene are associated with apathy in persons with AD. Each *OXTR* polymorphism was considered the main independent variable for Aim 2 analyses. Logistic regression analyses were used to examine the extent to which each genotype was associated with the presence or absence of apathy as described in the Aim 1 analyses. Similarly, multiple regression analyses were conducted to determine whether a relationship exists between the *OXTR* polymorphisms and the severity of apathy.

Aim 3. Examine the extent to which severity of apathy influences functional status in persons with AD, after adjusting for AD severity. In the Aim 3 analyses, severity of apathy served as the primary independent variable. Multiple regression methods were used to determine the relationship of apathy severity on the outcome of functional status (as determined by the FAST stage score), controlling for AD severity (as determined by total SIB score). Multiple regression methods were also used to determine the impact of apathy severity on the outcome of

functional status (as determined by the FAC subscale scores, controlling for AD severity [as determined by total SIB score]).

CHAPTER 5: RESULTS

The purpose of this cross-sectional correlational descriptive study was to examine the extent to which individual and social environmental factors influence the presence and severity of apathy in persons with Alzheimer Disease (AD) by addressing the following specific aims: 1) Examine the extent to which individual characteristics (demographics and cognitive status) and social environment factors predict the severity of apathy in persons with AD, after adjusting for AD severity and *Apolipoprotein E-4 (APOE4)* status, 2) Examine the extent to which variations in the *Oxytocin Receptor (OXTR)* gene are associated with apathy in persons with AD, and 3) Examine the extent to which severity of apathy influences functional status in persons with AD, after adjusting for AD severity. The results of the analyses completed to address these aims are presented in the Sample and Key Variable Description and Results by Specific Aim sections of this chapter.

Sample and Key Variable Description

The results of the descriptive analysis are presented according to the elements of the NDB model. Background Factor variables include demographic characteristics, genotype, and cognitive abilities as measured by the Severe Impairment Battery (SIB). The Proximal Factor key variable is social environment and was measured using two strategies: 1) a categorical variable, and 2) Ambiance Scale (AS) data available for a subset (n=23) of the sample. The Need-Driven Behavior (NDB) key variable is apathy as measured by the Neuropsychiatric Inventory Apathy Subscale (NPI-Apathy). The Apathy Inventory (IA) provided a secondary measure of apathy and addressed emotional, behavioral and cognitive aspects of apathy, with data available for a subset (n=22) of the sample. Both the Functional Abilities Checklist (FAC)

and the Functional Assessment Staging of Alzheimer Disease (FAST) were used to assess function, another principle study variable.

Background Factors.

Demographic characteristics. Descriptive characteristics of the study sample (N=66) are presented in Table 4. The majority of the participants (69.7%, n=46) were female. Age ranged from 59 to 101 years, with a mean of 85.83 (SD=7.35) years. Most participants were of non-Hispanic white ethnicity (97%, n=64), with a single participant of African American ethnicity (1.5%, n=1). Educational preparation spanned a broad range, from elementary school only to doctoral preparation. An equal number of participants (48.5%, n=32) completed some education beyond the high school level compared to education ending at or before the high school level (48.5%, n=32).

Table 4. Sample Characteristics: Demographic Variables [N=66]

	Mean ± SD	Range
Age (Year)	85.83 yrs ± 7.35	59-101
	Frequency = n	Percent %
Gender		
Female	46	69.7
Male	20	30.3
Ethnicity		
Non-Hispanic White	64	97.0
African American	1	1.5
Not specified	1	1.5
Education (N=65)		
Don't know	1	1.5
Attended Grade School	1	1.5
Completed 8th Grade	10	15.2
Attended High School	6	9.1
Completed High School	15	22.7
Attended College	14	21.2
Associate Degree	6	9.1
Bachelor's Degree	6	9.1
Completed Some Post-Graduate Courses	2	3.0
Master's Degree	3	4.5
Doctoral Degree	1	1.5
Not specified	1	1.5

Genotype/genetic measurement. DNA sequence variants were genotyped in both the *APOE* and *OXTR* genes.

Apolipoprotein E (APOE). Table 6 provides a summary of allele and genotype frequencies for each single nucleotide polymorphism (SNP); not all genotype frequency categories sum to 66, as data for every SNP was not available for every participant. *APOE* genotype was derived from two SNPs (rs429358, rs7412). Two variables related to the *APOE* gene were calculated, including a categorical variable based on the six possible *APOE* genotypes (2/2, 2/3, 2/4, 3/3, 3/4, 4/4) as well as a variable based on the number of copies of the *APOE4* allele (0, 1, 2 alleles). A *t* test, without equal variances assumed, failed to reveal a statistically significant difference in number of *APOE4* alleles for men (M=.65, s=.862) and women (M=.63, s=.628), $t(23) = .095$, p=.925. However, among this sample, number of *APOE4* alleles and age at symptom onset were significantly correlated (F=9.886, df=2, p<.0001). Persons with 1 or 2 copies of the *APOE4* allele were significantly younger at the time of symptom onset than persons with 0 copies of the *APOE4* allele (See Table 5). Number of *APOE4* alleles was not significantly correlated with years since symptom onset (r=.137 p=.315), nor with the presence or absence of a formal diagnosis of AD ($t(51) = -.885$, p=.380).

Table 5. Age of Symptom Onset by Number of *APOE4* alleles

	Number of *APOE4* alleles		
	0 –*E4* alleles [n=28]	1- *E4* allele [n=22]	2- *E4* alleles [n=7]
Age of Onset Mean ± SD	82.00 (6.79)	78.82 (7.52)	69.00 (4.87)
F=9.886 (df=2), p<.0001			

Table 6. Allele and Genotype Frequencies.

Gene (SNP)	Genotype frequency [n=57]						Allele frequency		
	2/2	2/3	2/4	3/3	3/4	4/4	ε2	ε3	ε4
APOE (ε2/ε3/ε4)	0	2 (0.035)	1 (0.018)	26 (0.456)	21 (0.368)	7 (0.123)	3 (0.026)	75 (0.658)	36 (0.316)

Gene (SNP)	Genotype frequency [n=62]			Allele frequency	
	CC	CT	TT	C	T
OXTR1 rs237895	25 (0.403)	28 (0.452)	9 (0.145)	78 (0.629)	46 (0.371)

Gene (SNP)	Genotype frequency [n=60]			Allele frequency	
	GG	AG	AA	G	A
OXTR2 rs53576	31 (0.517)	24 (0.400)	5 (0.083)	86 (0.717)	34 (0.283)

Gene (SNP)	Genotype frequency [n=64]			Allele frequency	
	GG	GT	TT	G	T
OXTR3 rs237885	14 (0.219)	35 (0.547)	15 (0.234)	63 (0.492)	65 (0.508)

Gene (SNP)	Genotype frequency [n=64]			Allele frequency	
	CC	AC	AA	C	A
OXTR4 rs6770632	44 (0.688)	15 (0.234)	5 (0.078)	103 (0.805)	25 (0.195)

Gene (SNP)	Genotype frequency [n=64]			Allele frequency	
	CC	CT	TT	C	T
OXTR5 rs2268491	47 (0.734)	15 (0.234)	2 (0.031)	109 (0.852)	19 (0.148)

Oxytocin Receptor (OXTR) gene. Table 6 provides a summary of allele and genotype frequencies for each SNP within the *OXTR* gene. Each *OXTR* genotype was derived from an individual SNP. Chi-squared tests were performed based on a binary variable indicating presence or absence of the minor allele for each *OXTR* SNP and gender, in order for the test to meet the assumption that all expected frequencies ≥5. There were no differences in allele or genotype frequency by gender across all 5 *OXTR* variants (data not shown).

Relationships among APOE4 and OXTR genotypes. The *OXTR* SNPs were selected, in part, to span the *OXTR* gene. Consequently, the relationships among *OXTR* genotypes demonstrate varied levels of linkage disequilibrium (see Table 7). *OXTR1* genotype had a strong significant correlation with *OXTR2* (r=.789, p<.0001) genotype and a moderately significantly correlation with *OXTR3* (r=.399, p=.001) genotype. However, *OXTR1* genotype was not significantly correlated with *OXTR4* (r=-.002, p=.985) or *OXTR5* (r=-.225, p=.079) genotypes. *OXTR2* genotype was moderately significantly correlated with both *OXTR3* genotype (r=.355, p=.005) and *OXTR5* genotype (r=-.257, p=.048), but not significantly correlated with *OXTR4* genotype (r=.084, p=.524). *OXTR3* genotype did not demonstrate a significant correlation with *OXTR4* genotype (r=-.088, p=.487) but did demonstrate a significant correlation with *OXTR5* genotype (r=.299, p=.016). Finally, no significant relationship (r=-.211, p=.094) emerged between *OXTR4* and *OXTR5* genotypes. As expected, given their location on different chromosomes, there were no significant correlations between number of *APOE4* alleles and genotype status for each of the five *OXTR* SNPs.

Cognitive abilities. Descriptive results related to cognition in this cross-sectional correlational descriptive study are presented in Table 8. Among this sample, age of onset of dementia symptoms ranged from 45 to 97 years, with a mean of 77.50 (SD=9.64) years. Only

two participants experienced the onset of dementia symptoms before age 60 years. There was a wide range in reported time since onset of symptoms (1-23 years) with a mean time since onset of 8.39 (SD=5.02) years. While all participants had a diagnosis and cognitive characteristics consistent with dementia, a formal diagnosis of AD, based on chart review and family report, was made for 60.6% (n=40) of the sample.

Table 7. *APOE4* and *OXTR* Genotype Correlations

	APOE4 alleles (p-value)	*OXTR1* (p-value)	*OXTR2* (p-value)	*OXTR3* (p-value)	*OXTR4* (p-value)	*OXTR5* (p-value)
APOE4 alleles		-.117 (.392)	-.181 (.195)	-.129 (.338)	.087 (.520)	.061 (.654)
OXTR1 rs237895			.789 (<.0001)**	.399 (.001)**	-.002 (.985)	-.225 (.079)
OXTR2 rs53576				.355 (.005)**	.084 (.524)	-.257 (.048)*
OXTR3 rs237885					-.088 (.487)	.299 (.016)*
OXTR4 rs6770632						-.211 (.094)
OXTR5 rs2268491						

All values denote Pearson Correlation (Significance 2-tailed) unless otherwise specified
** Significant at the p=0.05 level (2-tailed)*
***Significant at the p=0.01 level (2-tailed)*

The Severe Impairment Battery (SIB) served as the primary measure of cognition in this study (Panisset et al., 1994). The SIB, as a whole, demonstrated excellent internal consistency for the 51 items (Cronbach's alpha=.989) among the 65 participants for whom SIB data were available. The cognitive characteristics of the sample suggested moderate impairment, as evidenced by a mean total SIB score of 50.66 (SD=39.09; range=0-100). A comparison of the

median, 25th and 75th percentile for cognition (as measured by SIB total score) by gender is presented in Table 9. While cognition scores for men (M=62.53, s=31.104) were higher than for women (M=45.76, s=41.253), the difference approached, but did not reach statistical significance ($t(44) = 1.788$, p=.081). There was no significant correlation between age and years since symptom onset (r=-.175, p=.167). In addition, the years since symptom onset did not differ for males (M=7.21, s=4.906) and females (M=8.89, s=50.42), $t(62) = -1.226$, p=.225. Finally, there was no statistically significant difference in cognition (SIB total score) for persons with a formal diagnosis of AD (M=51, s=37.940) compared to those without a formal diagnosis of AD (M=45.90, s= 42.057), $t(58) = -.478$, p=.635.

Table 8. Descriptive Results Related to Cognition [N=66]

	Mean ± SD	Range
Age of Symptom Onset	77.50 yrs ± 9.64	45-97
Years Since Symptom Onset	8.39 yrs ± 5.02	1-23
SIB Total Score (possible: 0-100*)	50.66 ± 39.087	0-100
	Frequency = n	Percent %
Formal AD Diagnosis Made		
No	21	31.8
Yes	40	60.6
Don't Know	4	6.1
Not specified	1	1.5

** Lower scores indicate more compromised cognitive function*
SIB = Severe Impairment Battery

Table 9. Cognition (as Measured by SIB total score) by Gender [n=65]

	Gender	
SIB Score (range= 0-100*)	Women [n=46]	Men [n=19]
Mean (SE)	45.76 (6.08)	62.53 (7.14)
Median	40	73
25th percentile	2	54
75th percentile	90	85
Interquartile Range	88	31

** Lower scores indicate more compromised cognitive function*
SIB = Severe Impairment Battery

Proximal Factors.

Social environment. Social environment was measured using both a categorical variable based on place of residence at time of data collection and the Ambiance Scale (AS).

Place of residence. Descriptive results related to social environment are presented in Table 10. The primary measure of social environment was based on residence at the time of data collection. Several participants (63.6%, n=42) resided in an extended or long-term care facility (ECF/LTC) or nursing home with a dementia-specific care unit at the time of data collection. Others resided in an ECF/LTC facility or nursing home (25.8%, n=17), assisted living or adult foster care (3.0%, n=2), or in their own homes (7.6%, n=5). No participants in this sample resided in a family member's home or in an assisted living or adult foster care setting with a dementia specific unit. For further analyses, categories were collapsed into two groups: dementia-specific environment and non dementia-specific environment. The collapsed dementia-specific environment group encompassed individuals dwelling in their own home or in an ECF/LCF or nursing home with a dementia-specific care unit. The non dementia-specific environment group encompassed those living in assisted living or adult foster care as well as those dwelling in an ECF/LTC facility or nursing home. Because an individual's own home is more individually tailored and familiar, more like a dementia-specific care unit, individuals dwelling in their own homes were included within the dementia-specific environment group in an effort to capture characteristics of the social environment. Using this categorization, 71.2% (n=47) of participants resided in an environment designed for persons with dementia.

Participant place of residence at time of data collection did not significantly differ by gender (X^2 [1, N=66] =.021, p=.886), age (t(63) =1.369, p=.176), age at symptom onset (t(62) = 1.809, p=.075), or time since symptom onset (t(55) =-1.637, p=.107). In addition, presence of a

formal AD diagnosis (X^2 (1, N =61) =1.666, p=.197) and level of cognitive impairment (t(63) =-.351, p=.218) did not differ according to whether or not participants resided in a dementia-specific care setting. Please see Table 11 for mean differences by place of residence.

Table 10. Descriptive Results Related to Social Environment - Place of Residence [N=66]

	Frequency = n	Percent %
Place of Residence		
Own Home	5	7.6
Assisted Living/Adult foster care	2	3.0
ECF/LTC/Nursing home	17	25.8
ECF/LTC/Nursing home – Dementia specific unit	42	63.6
New Residence (+/- dementia-specific)		
Dementia-Specific Residence	47	71.2
Non Dementia-Specific Residence	19	28.8
Ambiance Scale total score [n=23] (range= -24 - +24, transformed to 0 - 1*) Mean ± SD (range)	0.484 ± 0.143 (0.24-0.80)	

**Lower scores indicate a more embellished, stimulating, unpretentious, colorful, warm, peaceful, welcoming, informal and novel environment*
Note: ECF = Extended Care Facility, LTC= Long Term Care Facility

Table 11. Mean Differences in Demographic and Cognitive Characteristics for Total Sample by Place of Residence [N=66]

	Dementia-Specific Residence Mean ± SD	Non Dementia-Specific Residence Mean ± SD
Age [n=64]	85.06 (7.63)	87.83 (6.34)
Age at Symptom Onset [n=64]	76.21 (10.27)	81.06 (6.65)
Time Since Symptom Onset [n=64]	8.85 (5.57)	7.12 (2.80)
Cognition as measured by SIB (possible: 0-100*) [n=65]	51.72 (40.25)	47.89 (36.83)

** Lower scores indicate more compromised cognitive function, SIB = Severe Impairment Battery*

Ambiance Scale (AS). The Ambiance Scale (AS) served as a secondary measure of social environment, with data available for a subset of the sample (n=23). The instrument includes thirteen adjective pairs, which are formatted using a revised semantic differential scaling model

(+2 to -2), resulting in a possible scoring range from +26 to -26 (Algase et al., 2007). In order to enhance interpretability, scores were summed and transformed to values 0 to 1. Values closer to 0 denote more embellished, stimulating, unpretentious, colorful, warm, peaceful, welcoming, informal and novel spaces. A value of 1 represents a living space that is stark, custodial, pretentious, drab, cold, chaotic, impersonal, formal and boring. The AS demonstrated good internal consistency (Cronbach's alpha=0.881) for the nine items among the subsample of 23 participants for whom AS data were available. The mean ambiance (AS total score) of the rooms within which participants resided was 0.484 (SD=0.143; range=0.24-0.80) suggesting moderately embellished, stimulating, unpretentious, colorful, warm, peaceful, welcoming, informal and novel living spaces for participants in this sub sample (See Table 10).

Social environment as measured by AS total score demonstrated few significant relationships with other study variables. AS total score did not significantly differ by gender ($t(21) = -.726$, $p = .476$). Social environment as measured by AS total score was not significantly correlated with age at symptom onset (r=.067, p=.767) nor time since symptom onset (r=.027, p=.907). A *t* test, with equal variances assumed, failed to reveal a statistically significant difference in AS total score for persons with and without a formal AD ($t(18) = -.153$, $p = .880$). Social environment as measured by AS total score was not significantly correlated with cognition (SIB total score) (r=-.170, p=.439).

Relationships among measures of social environment. Data for social environment as measured by both residence at time of data collection and AS total score were available for a subset of the population (n=23). A *t* test, with equal variances assumed, failed to reveal a statistically significant difference in ambiance (AS total score) for persons residing in a dementia-specific care unit (M=.450, s=.122) compared to non dementia-specific care units

(M=.547, s=.1650), $t(21) = 1.602$, p=.124. Social environment as measured by residence at time of data collection and social environment as measured by AS total score were not significantly correlated (r=-.330, p=.124) among this subsample.

Need Driven Behavior (NDB) (Outcome Variable).

Behavioral symptoms. Study participants demonstrated a notable prevalence of behavioral symptoms as measured by the Neuropsychiatric Inventory – Nursing Home version (NPI-NH). Among persons for whom NPI-NH data were available, 93% (n=57) exhibited at least one behavioral symptom. Apathy (n=35, 53%), Agitation/Aggression (n=35, 53%), and Irritability/Lability (n=31, 47%) were the most frequently exhibited behavioral symptoms (see Table 12), with apathy the primary need driven behavior (NDB) of interest in this study. While comprehensive analyses of behavioral symptoms were not the focus of this study, correlations between apathy and depression were examined. Depression (NPI-Depression) was not significantly correlated with apathy (NPI-Apathy) (n=56, r=-.054, p=.690) nor apathy as measured by IA total score (n=21, r-.243, p=.289).

Table 12. Behavioral Symptom Frequencies (NPI-NH) [n=57]

	Frequency = n	Percent %
Behavioral Symptom		
Delusions	13	19.7
Hallucinations	11	16.7
Agitation/Aggression	35	53.0
Depression	16	24.2
Anxiety	13	19.7
Elation/Euphoria	2	3.0
Apathy/Indifference	35	53.0
Disinhibition	12	18.2
Irritability/Lability	31	47.0
Aberrant Motor Behavior	18	27.3
Night-time Behavior	9	13.6
Appetite/Eating Change	17	25.8

NPI-NH = Neuropsychiatric Inventory-Nursing Home

Apathy. The Neuropsychiatric Inventory Apathy Subscale (NPI-Apathy) served as the primary measure of apathy in this study (Cummings et al., 1994; Wood et al., 2000) and provided an indication of the presence of apathy (NPI-Apathy binary variable) as well as apathy severity (NPI-Apathy frequency x severity). The Apathy Inventory (IA) served as a secondary measure of apathy, with data available for a subset (n=22) of the sample (Robert et al., 2002). See Table 13 for apathy prevalence and severity according to the NPI-Apathy and IA instruments

Presence of apathy.

Presence of apathy (NPI-Apathy). The prevalence of apathy among this sample was 53% (n=35). By gender, 53.66% (n=22) of women and 81.25% (n=13) of men exhibited apathy. While the percentage of men with apathy was higher than the percentage of women with apathy, this difference approached, but was not, statistically significant [X^2 (1, N= 57) =3.697, p=.055].

The extent to which the presence of apathy differed according to other demographic or disease characteristics was also explored (see Table 14). For example, presence or absence of apathy (NPI-Apathy) did not significantly differ by age (t(55) =-.951, p=.346), age at symptom onset (t(54) =-.939, p=.352), years since symptom onset (t(54) =.558, p=.579) or formal diagnosis of AD (X^2 (1, N=53) =.003, p=.954). A t test, with equal variances assumed, did not reveal a statistically significant difference in cognition (SIB total score) between persons exhibiting and not exhibiting apathy (NPI-Apathy) (t(55) =1.652, p=.104). Residence at time of data collection and presence of apathy (NPI-Apathy) did not demonstrate a significant relationship, X^2 (1, N=57) =.249, p=.618. There was also no significant difference in AS total score between persons exhibiting and not exhibiting apathy (NPI-Apathy) (t(20) =.413, p=.684).

Table 13. Apathy Prevalence and Severity according to the NPI and IA Instruments.

	Frequency = n	Percent %
Apathy Presence (NPI-Apathy) [n=57] Yes No	 35 22	 53.0 33.3
Apathy Severity (NPI-Apathy Frequency x Severity Score) [n=57] (range= 0-12*) Mean ± SD (range)	5.02 ± 4.952 (0-12)	
Apathy Presence (IA) [n=22] Yes No	 16 6	 72.7 27.3
Apathy Severity (IA Total Score) [n=22] (range= 0-36*) Mean ± SD (range)	11.27 ± 12.597 (0-36)	

** Lower scores indicate less apathy*
NPI = Neuropsychiatric Inventory
IA = Apathy Inventory

Table 14. Mean Differences in Demographic and Cognitive Characteristics by Presence of Apathy (NPI-Apathy) [n=57]

	Participants Exhibiting Apathy (NPI-Apathy) Mean ± SD	Participants Not Exhibiting Apathy (NPI-Apathy) Mean ± SD
Age	86.89 (6.30)	85.05 (8.26)
Age at Symptom Onset	78.77 (7.57)	76.33 (11.90)
Time Since Symptom Onset	8.11 (3.89)	8.86 (6.09)
Cognition as measured by SIB	45.17 (37.94)	62.45 (39.25)
Social Environment as measured by Ambiance Scale	.482 (.118)	.507 (.168)

** Significant at the p=0.05 level (2-tailed)*
*** Significant at the p=0.01 level (2-tailed)*
NPI = Neuropsychiatric Inventory
SIB = Severe Impairment Battery

Presence of apathy (IA). A larger proportion of participants from this subsample (72.72%, n=16) exhibited apathy as measured by the IA (see Table 15) compared to those participants exhibiting apathy as measured by the NPI-Apathy (53%, n=35). By gender among this subsample, 64.29% (n=9) of women and 87.5% (n=7) of men exhibited apathy as measured by the IA binary variable. A Fisher's exact test was performed to confirm whether presence of

apathy significantly differed by gender, as some cells had an expected count less than 5. Presence or absence of apathy as measured by the IA binary variable did not significantly differ by gender (p=.351).

The extent to which the presence of apathy differed according to other demographic or disease characteristics was also explored (see Table 15). For example, a *t* test, without equal variances assumed, failed to reveal a statistically significant difference in age for person exhibiting and not exhibiting apathy (IA) ($t(5) = -1.414$, p=.212). Presence or absence of apathy did not differ by age at symptom onset ($t(5) = -1.051$, p=.337), years since symptom onset ($t(20) = .396$, p=.697), or formal diagnosis of AD (Fisher's exact, p=.613). There was, however, a significant relationship between cognition as measured by SIB total score and presence of apathy (IA) ($t(16) = 3.397$, p=.004). Residence at time of data collection and presence of apathy (IA) did not demonstrate a significant relationship (Fisher's exact, p=.585). Finally, there was no significant difference in AS total score between persons exhibiting and not exhibiting apathy ($t(18) = .081$, p=.936).

Table 15. Mean Differences in Demographic and Cognitive Characteristics by Presence of Apathy (IA) [n=22]

	Participants Exhibiting Apathy (IA) Mean ± SD	Participants Not Exhibiting Apathy (IA) Mean ± SD
Age	87.25 (4.14)	80.00 (12.30)
Age at Symptom Onset	79.63 (6.61)	71.33 (18.90)
Time Since Symptom Onset	7.63 (4.52)	8.67 (7.74)
Cognition as measured by SIB	69.63 (30.31)	96.00 (4.15)
Social Environment as measured by Ambiance Scale	.470 (.137)	.476 (.154)

** Significant at the p=0.05 level (2-tailed)*
*** Significant at the p=0.01 level (2-tailed)*
IA = Apathy Inventory
SIB = Severe Impairment Battery

Severity of apathy.

Severity of apathy (NPI-Apathy). A mean NPI-Apathy frequency x severity score of 5.02 (SD=4.952; range=0-12) suggested moderate severity of apathy among this sample. The median, 25th and 75th percentile for apathy as measured by the NPI-Apathy frequency x severity score by gender is presented in Table 16).

Table 16. Apathy Prevalence and Severity (as Measured by NPI-Apathy) by Gender [n=57]

	Gender	
	Women [n=41]	Men [n=16]
Apathy Presence (NPI-Apathy)	n (%)	n (%)
Yes	22 (53.66)	13 (81.25)
No	19 (46.34)	3 (18.7)
Apathy Severity (NPI-Apathy FxS Score) (range= 0-12*)		
Mean (SE)	4.80 (.814)	5.56 (1.080)
Median	4	5
25th percentile	0	1.5
75th percentile	12	8
Interquartile Range	12	7

** Lower scores indicate less apathy*
FxS= Frequency by Severity
NPI = Neuropsychiatric Inventory
SIB = Severe Impairment Battery

Please see Table 17 for additional correlations among variables. There were no significant correlations between severity of apathy as measured by the NPI-Apathy and age (r=.211, p=.116), age at symptom onset (r=.107, p=.431), or years since symptom onset (r=.091, p=.505). Additionally, severity of apathy (NPI-Apathy) did not significantly differ between persons formally diagnosed with AD (M=5.22, s=4.876) and persons lacking a formal AD diagnosis (M=5.71, s=5.241), $t(51) = .329$, p=.743. There was a moderately significant relationship (r=-.380, p=.004) between level of cognitive impairment and apathy severity.

Specifically, participants with more compromised cognitive function (lower SIB total score) were more likely to demonstrate more severe apathy compared to subjects with higher cognitive function. Apathy severity (NPI-Apathy) did not significantly differ among persons dwelling in a non-dementia specific care residence (M=4.88, s=5.201) and dementia-specific care residence or home setting (M=5.07, s=4.916), *t*(55)= -.135, p=.893. Likewise, apathy severity and social environment as measured by AS total score were not significantly correlated (p=.094, p=.677).

The NPI-NH provides an opportunity for caregivers to rate the disruption of behavioral symptoms exhibited by persons with dementia. Interestingly, apathy disruption scores were quite low among caregivers of persons with dementia in this sample. Frequencies for caregiver reported apathy disruption scores for the 35 participants exhibiting apathy (NPI-Apathy) are depicted in Table 18.

Table 17. Relationship between Demographic Characteristics, Cognitive Characteristics, and Apathy Severity (as Measured by NPI-Apathy) – Correlations [n=57]

	Apathy Severity NPI-Apathy FxS Score (p-value)
Age	.211 (.116)
Age at Symptom Onset	.107 (.431)
Time Since Symptom Onset	.091 (.505)
Cognition as measured by SIB	-.380 (.004)**
Social Environment as measured by Ambiance Scale	.094 (.677)

** Significant at the p=0.05 level (2-tailed)*
*** Significant at the p=0.01 level (2-tailed)*
FxS= Frequency by Severity
NPI = Neuropsychiatric Inventory
SIB = Severe Impairment Battery

Table 18. Apathy Disruption Scores for Persons Exhibiting Apathy (NPI) [n=35]

NPI-Apathy Disruption Score	Not at All	Minimally	Mildly	Moderately	Severely	Very severely or extremely	Total
n	12	9	5	3	3	3	35
(%)	(34.3)	(25.7)	(14.3)	(8.6)	(8.6)	(8.6)	(100)

NPI = Neuropsychiatric Inventory

Severity of apathy (IA total score). The severity of apathy as measured by a mean IA total score of 11.27 (SD=12.597; range=0-36) also suggested moderate severity of apathy among the subsample of 23 participants. The median, 25th and 75th percentile for apathy as measured by the IA total score by gender is presented in Table 19. While the percentage of men with apathy was higher than the percentage of women with apathy, this difference was not statistically significant ($t(20) = .338$, $p = .739$).

Table 19. Apathy Prevalence and Severity (as Measured by IA Total Score) by Gender [n=22]

	Gender	
	Women [n=14]	Men [n=8]
Apathy Prevalence Yes No	n (%) 9 5	n (%) 7 1
Apathy Severity (range= 0-36*) Mean (SD)	10.57 (14.092)	12.5 (10.226)
Mean (SE)	10.57 (3.766)	12.5 (3.615)
Median	3.5	12.5
25th percentile	0	3.25
75th percentile	27.5	20
Interquartile Range	28	17

** Lower scores indicate less apathy*
IA = Apathy Inventory

Please see Table 20 for additional correlations among variables, with relationships essentially the same as those identified with the use of the NPI- Apathy. Apathy severity as measured by IA total score was not significantly correlated with age (r=-.232, p=.299), age at symptom onset (r=.209, p=.350) or years since symptom onset (r=-.112, p=.620).

The significant relationship between cognition as measured by SIB total score and apathy severity as measured by IA total score was also evident in this smaller subset (r=-.513, p=.015). A *t* test, with equal variances assumed, failed to reveal a statistically significant difference in apathy severity (IA total score) between persons with a formal AD diagnosis (M=14.00, s=13.121) and without a formal AD diagnosis (M=8.00, s=12.215), *t*(18)=-.955, p=.352. Apathy severity (IA total score) did not significantly differ among persons dwelling in non-dementia specific care residence (M=9.40, s= 5.159) and those dwelling in dementia-specific care residence or the home setting (M=11.82, s=12.223), *t*(20)=-.370, p=.715. Finally, apathy severity and social environment as measured by AS total score were not significantly correlated (r=.101, p=.672).

Severity of apathy (IA subscales). The IA instrument contains three subscales including Lack of Interest, Emotional Blunting and Lack of Initiative (Robert et al., 2002). Relationships were examined among severity scores for each IA subscale and the following variables: gender, age, age at symptom onset, time since symptom onset, presence of formal diagnosis of AD, cognition as measured by SIB total score, social environment as measured by residence at time of data collection and social environment as measured by AS total score (see Table 20). Significant relationships were largely consistent with those examined using the apathy severity as measured by IA total score. For example, cognition was significantly correlated with apathy severity across all domains of apathy: Emotional Blunting (r=-.458, p=.032), Lack of Initiative

(r=-.433, p=.044), Lack of Interest (p=-.504, p=.017). Participants who scored lower on the SIB, indicating more compromised cognition, had significantly higher apathy scores as measured by each of the IA subscales. Associations between apathy (IA subscales) and categorical variables (gender, formal AD diagnosis, residence) were not significant (Data not shown).

Table 20. Relationships among Demographic Characteristics, Cognitive Characteristics, and Apathy Severity (as Measured by IA Total Score) [n=22]

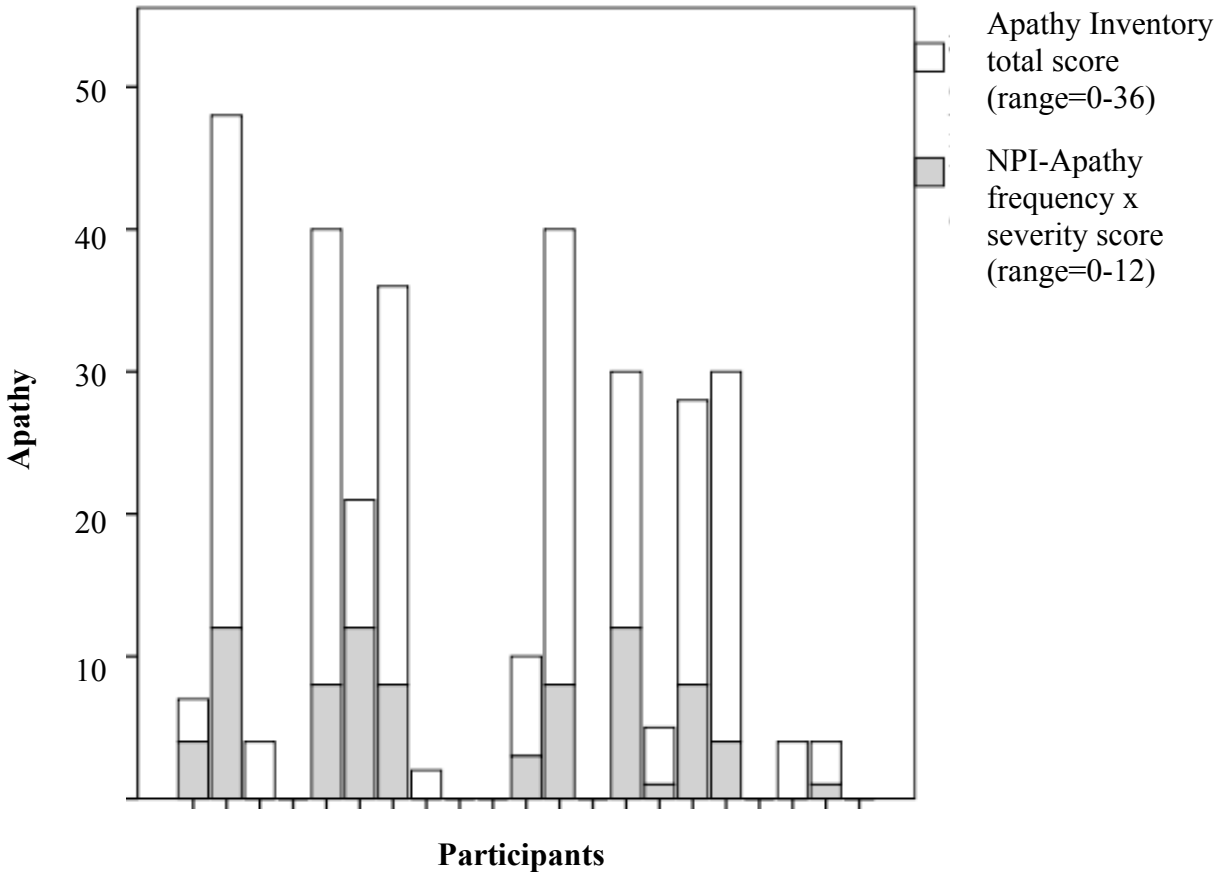
	IA Total Score Pearson Correlation (p-value)	IA Emotional Blunting FxS Pearson Correlation (p-value)	IA Lack of Initiative FxS Pearson Correlation (p-value)	IA Lack of Interest FxS Pearson Correlation (p-value)
Age	.232 (.299)	.141 (.532)	.146 (.517)	.339 (.122)
Age at Symptom Onset	.209 (.350)	.128 (.570)	.148 (.511)	.287(.195)
Time Since Symptom Onset	-.112 (.620)	-.070 (.755)	-.105 (.641)	-.124 (.582)
Cognition as measured by SIB	-.513 (.015)*	-.458 (.032)*	-.433 (.044)*	-.504 (.017)*
Social Environment as measured by Ambiance Scale	.101 (.672)	.165 (.488)	-.047 (.845)	.165 (.487)

** Significant at the p=0.05 level (2-tailed)*
*** Significant at the p=0.01 level (2-tailed)*
FxS= Frequency by Severity
IA = Apathy Inventory
SIB = Severe Impairment Battery

Relationships among measures of apathy. Among the subset of the sample (n=21) with data available for both the IA and NPI-Apathy, apathy was identified among 57.1% (n=12) of the sample as measured by the NPI-Apathy binary variable and among 71.4% (n=15) of the sample as measured by the IA binary variable. Each participant who endorsed apathy according to the NPI-Apathy binary variable also endorsed apathy according to the IA binary variable

(see Figure 3). However, three additional participants were identified as having apathy using the IA binary variable as compared to the NPI-Apathy binary variable.

Figure 3. Apathy as Measured by Apathy Inventory Total Score and NPI-Apathy Frequency x Severity Score [n=21]



While data for both the IA and NPI-Apathy were only available for a subset of the population (n=21), significant relationships were demonstrated among variables. Subsets were deemed sufficiently similar to support comparing instruments between the two subsets. As depicted in Table 21, a *t* test, without equal variances assumed, revealed a statistically significant difference in apathy severity (IA Emotional Blunting subscale) among persons exhibiting and not

exhibiting apathy (NPI-Apathy) (t(11.7) =-.3.909, p=.002). There was also a statistically significant difference in apathy severity (IA Lack of Initiative subscale) among persons exhibiting and not exhibiting apathy (NPI-Apathy) (t(13.4) =-.3.180, p=.007).

There was a statistically significant difference in apathy severity (IA Lack of Interest subscale) among persons exhibiting and not exhibiting apathy (NPI-Apathy) (t(11) =-.5.498, p<.0001). Presence of apathy as measured by the NPI-Apathy and severity of apathy as measured by the IA Lack of Interest subscale demonstrated the strongest relationship (t=-.5.498, p<.0001). Finally, presence of apathy (NPI-Apathy) and severity of apathy as measured by IA total score demonstrated a significant relationship (t(11.6) =-.4.648, p=.001).

Table 21. Presence of Apathy (NPI-Apathy) and Apathy Severity (IA Subscales) [n=21]

	Participants Exhibiting Apathy (NPI-Apathy) Mean ± SD	Participants Not Exhibiting Apathy (NPI-Apathy) Mean ± SD
Apathy Severity** IA Emotional Blunting Subscale	5.33 (4.36)	0.33 (.707)
Apathy Severity** IA Lack of Initiative Subscale	5.92 (5.30)	0.78 (1.56)
Apathy Severity** IA Lack of Interest Subscale	6.92 (4.36)	0.00 (.000)
IA Total Score **	18.17 (12.55)	1.11 (1.76)

** Significant at the p=0.05 level (2-tailed)*
*** Significant at the p=0.01 level (2-tailed)*
NPI = Neuropsychiatric Inventory
IA = Apathy Inventory

As detailed in Table 22, apathy severity as measured by the NPI-Apathy frequency x severity score, demonstrated strong significant positive correlations with frequency x severity scores for each of the IA subscales: Emotional Blunting (r=.734, p<.0001), Lack of Initiative (r=.624, p=.002), Lack of Interest (r=.834, p<.0001). Apathy severity as measured by the NPI-

Apathy and apathy severity as measured by IA total score also demonstrated a highly significant relationship (r=.786, p<.0001).

Table 22. Relationships Among Measures of Apathy [n=21]

	IA Total Score (p-value)	IA Emotional Blunting FxS (p-value)	IA Lack of Initiative FxS (p-value)	IA Lack of Interest FxS (p-value)
NPI-Apathy FxS Score	.786 (<.0001)**	.734 (<.0001)**	.624 (.002)**	.834 (<.0001)**

All values denote Pearson Correlation (Significance 2-tailed) unless otherwise specified
** Significant at the p=0.05 level (2-tailed)*
*** Significant at the p=0.01 level (2-tailed)*
NPI = Neuropsychiatric Inventory
IA – Apathy Inventory
FxS= Frequency by Severity

Binary variables representing presence of apathy as measured by the IA and presence of apathy as measured by the NPI-Apathy demonstrated a significant relationship (Fisher's exact, p=.002). These relationships support the construct validity of the IA, when compared to the NPI-Apathy. Additionally, analyses demonstrated that the IA, as compared to the NPI-Apathy, categorized more people as apathetic in this sample.

The IA demonstrated excellent internal consistency (Cronbach's alpha= .886, n=3), based on frequency x severity scores for each of the three IA subscales among the subsample of 22 participants for whom IA data were available. The IA Emotional Blunting frequency x severity scores were highly significantly correlated with both the IA Lack of Initiative frequency x severity score (r=.823, p<.0001) and the IA Lack of Interest frequency x severity scores (r=.731, p<.0001). The IA Lack of Initiative frequency x severity scores and IA Lack of Interest frequency x severity scores were also highly significantly correlated (r=.644, p=.001). Finally, the IA Total scores were highly significantly correlated with frequency x severity scores for each

of the IA subscales: Emotional Blunting (r=.933, p<.0001), Lack of Initiative (r=.912, p<0001), Lack of Interest (r=.874, p<.0001).

Function.

Functional Assessment Staging (FAST) tool. The Functional Assessment Staging Tool (FAST) (Reisberg et al., 1985) was used as the primary measure of function in this dissertation project. Among this sample, functional limitations ranged from 3, indicating 'Decreased job functioning evident to coworkers; difficulty in traveling to new locations' to 7f, indicating 'Unable to hold head up'. The mean score was 6e, which represents 'Fecal incontinence, occasional or more frequent'. The median, 25th and 75th percentile for function as measured by the FAST by gender is presented in Table 23. Mean and median scores were similar for both genders, and a *t* test, with equal variances assumed, failed to reveal a statistically significant difference in mean FAST score by gender ($t(64) = -.266$, p=.791).

Table 23. Comparison of Functional Status by Gender using FAST scale [N=66]

	Gender	
FAST score (range= 1-7f*, numerically represented as 1-16*) Mean (SD)	Women [n=46] 10.13 (3.257)	Men [n=20] 9.90 (3.177)
Mean (SE)	10.13 (.480)	9.90 (.710)
Median	10.00	10.00
25th percentile	8.00	9.00
75th percentile	13.00	12.75
Interquartile Range	5	4

** Lower scores indicate less compromised function*
FAST = Functional Assessment Staging Tool

Additional relationships related to function as measured by FAST score are recorded in Table 24. Function as measured by FAST score was not significantly correlated with age (r=.017, p=.891), age at symptom onset (r=-.065, p=.609) nor years since symptom onset

(r=.147, p=.247). A *t* test, with equal variances assumed, failed to reveal a statistically significant difference in function (FAST score) between persons with a formal AD diagnosis (M=10.30, s=3.196) and those without a formal AD diagnosis (M=9.52, s=3.386), *t*(59)=-.883, p=.381.

There was a highly significant (r=-.704, p<.0001) relationship between cognition and function as measured by the FAST. Persons who scored lower on the SIB, indicating more severe cognitive impairment, scored higher on the FAST, indicating more severe functional impairment. Functional status did not significantly differ among persons dwelling in non-dementia specific care residence (M=10.79, s=3.029) and those dwelling in dementia-specific care residence or the home setting (M=9.77, s=3.265), *t*(64)=1.176, p=.244. Nor was there a significant correlation between function (FAST score) and social environment as measured by the AS (r=.325, p=.130).

FAST score and presence of apathy. Significant relationships existed between function as measured by FAST score and all measures of apathy. Function (FAST score) significantly differed among persons exhibiting apathy according to the NPI-Apathy (M= 0.89, s=2.784) and those not exhibiting apathy according to the NPI-Apathy (M=8.55, s=3.143), *t*(55) =-2.939, p=.005. Function (FAST score) also significantly differed among persons exhibiting apathy according to the IA (M=9.81, s=3.103) and those not exhibiting apathy according to the IA (M=5.50, s=2.881), *t*(20) =-2.955, p=.008.

FAST score and severity of apathy. Function as measured by FAST score was significantly correlated with apathy severity when measured both by NPI-Apathy frequency x severity score (r=.453, p<.0001) and by the IA total score (r=.579, p=005). Significant relationships were also identified between apathy severity and function (FAST score) across all three apathy domains: Emotional Blunting (r=.540, p=.009), Lack of Initiative (r=.483, p=.023),

Lack of Interest (r=.554, p=.007). In each case, participants displaying higher FAST scores, indicating greater functional deficits, also displayed a higher prevalence and severity of apathy as measured by both the NPI-Apathy and IA.

Table 24. Relationships among Demographic Characteristics, Cognitive Characteristics, and Function (as Measured by FAST score and FAC Subscales)

	FAST score (p-value)	FAC Self Care (p-value)	FAC Inapp. Behavior (p-value)	FAC Cognitive Status (p-value)	FAC Agitation (p-value)
Age	.017 (.891)	.045 (.720)	-.058 (.649)	.086 (.495)	-.010 (.939)
Age at Symptom Onset	-.065 (.609)	.047 (.710)	-.117 (.357)	.110 (.386)	.001 (.993)
Time Since Symptom Onset	.147 (.247)	-.017 (.893)	.146 (.250)	-.082 (.519)	-.017 (.897)
Cognition as measured by SIB	-.704 (<.0001)**	-.537 (<.0001)**	-.283 (.022)*	-.668 (<.0001)**	.132 (.294)
Social Environment as measured by AS	.325 (.130)	.193 (.379)	.508 (.013)*	.318 (.140)	-.040 (.857)
Apathy as measured by NPI-Apathy FxS score	.452 (<.0001)**	.325 (.014)*	.105 (.435)	.448 (<.0001)**	-.324 (.014)*
Apathy as measured by IA total score	.579 (.005)**	.397 (.067)	.229 (.305)	.449 (.036)*	-.257 (.248)
IA Emotional Blunting FxS	.540 (.009)**	.303 (.171)	.265 (.233)	.358 (.102)	-.261 (.241)
IA Lack of Initiative FxS	.483 (.023)*	.386 (.076)	.127 (.573)	.386 (.076)	-.253 (.257)
IA Lack of Interest FxS	.554 (.007)**	.382 (.080)	.242 (.279)	.471 (.027)*	-.188 (.403)

** Significant at the p=0.05 level (2-tailed)* *FxS= Frequency by Severity*
*** Significant at the p=0.01 level (2-tailed)* *IA = Apathy Inventory*
SIB = Severe Impairment Battery *FAST = Functional Assessment Staging Too*
AS= Ambiance Scale *FAC = Functional Abilities Checklist*
NPI = Neuropsychiatric Inventory

Functional Abilities Checklist (FAC). The Functional Abilities Checklist (FAC) served as a secondary measure of function in this dissertation study. The 28-item FAC measures four domains of the functional abilities of persons with AD: 1) self-care ability; 2) inappropriate behavior; 3) cognitive status; and 4) agitated behavior (Maas & Buckwalter, 1990). Data were analyzed by calculating a mean total score for each of the four subscales as advised by FAC authors (D. A. Reed, personal communication, April 4, 2013). Based on mean total scores for each subscale (see Table 25), this sample demonstrated the most compromised function in the self-care domain as measured by the self-care (FAC Self Care subscale: M=3.01, SD=.582; range=1.67-3.89) and the cognitive domain (FAC Cognitive Status subscale: M=3.24, SD=.918; range=1.00-4.00). Less compromised function was demonstrated within the two behavioral domains of function: 1) FAC Inappropriate Behavior subscale mean score 1.36 (SD=.463; range=1.00-3.00), and 2) FAC Agitation subscale mean score 1.52 (SD=.565; range=1.00-3.20).

Relationships were also examined between function, as measured by the FAC, and all key study variables. There were no statistically significant differences in function by gender across each of the IA subscales (See Table 25): Self Care ($t(64) = 1.529$, p=.131), Inappropriate Behavior ($t(64) = .833$, p=.408), Cognitive Status ($t(64) = 1.179$, p=.858), and Agitated Behavior ($t(64) = 1.270$, p=.209). In addition, there was no significant difference in function among persons with and without a formal AD diagnosis as measured by each of the IA subscales: Self Care ($t(59) = -.522$, p=.603), Inappropriate Behavior ($t(59) = .114$, p=.909), Cognitive Status ($t(59) = .237$, p=.813), and Agitated Behavior ($t(59) = -1.865$, p=.067).

Table 25. Functional Characteristics of the Sample [N=66]

	Mean ± SD	Range
FAST score (possible range= 1-7f*, numerically represented as 1-16*)	10.06 ± 3.21	3-16
FAC Self Care subscale mean score (possible range= 1-4*)	3.01 ± .582	1.67-3.89
FAC Inappropriate Behavior subscale mean score (possible range= 1-4*)	1.36 ± .463	1.00-3.00
FAC Cognitive Status subscale mean score (possible range= 1-4*)	3.24 ± .918	1.00-4.00
FAC Agitated Behavior subscale mean score (possible range= 1-4*)	1.52 ± .565	1.00-3.20

** Lower scores indicate less compromised function*
FAST = Functional Assessment Staging Tool
FAC = Functional Abilities Checklist

Table 26. Mean Function (FAC Subscales) by Gender [N=66]

	Males Mean ± SD	Females Mean ± SD
Self Care subscale	3.17 (.575)	2.94 (.577)
Inappropriate Behavior subscale	1.44 (.458)	1.33 (.467)
Cognitive Status subscale	3.21 (.923)	3.25 (.926)
Agitated Behaviors subscale	1.65 (.465)	1.46 (.599)

** Significant at the p=0.05 level (2-tailed)*
*** Significant at the p=0.01 level (2-tailed)*
FAC = Functional Abilities Checklist

Correlations between each of the FAC subscales and quantitative variables can be viewed in Table 26. Significant relationships began to emerge when examining function, as measured by the FAC, and cognition (SIB total score). A significant relationship was demonstrated between cognition and functional status as measured by each of the FAC subscales: Self Care (r=-.537, p<.0001), Inappropriate Behavior (r=-.283, p=.022), and Cognitive Status (r=-.668, p<.0001), with the exception of the Agitated Behaviors subscale (r=.132, p=.294). Higher scores on the

Self Care, Inappropriate Behavior, and Cognitive Status subscales of the FAC, indicating more compromised functional status, were significantly correlated with more compromised cognition and lower SIB total scores.

Function, as measured by each of the FAC subscales, did not significantly differ among persons dwelling in dementia and non-dementia specific residence: Self Care subscale ($t(64)=.534$, p=.595), Inappropriate Behaviors subscale ($t(64) =.387$, p=.700), Cognitive Status subscale ($t(64)=.566$, p=.573), and Agitated Behaviors subscale $t(64) = -.072$, p=.943). Social environment as measured by AS was significantly correlated with function as measured by the FAC Inappropriate Behaviors subscale (r=.508, p=.013). More severe functional deficit (FAC Inappropriate Behaviors subscale) was associated with a living space that was stark, custodial, pretentious, drab, cold, chaotic, impersonal, formal and boring, as measured by the AS. Social environment as measured by the AS did not demonstrate a significant relationship with function as measured by the three remaining FAC subscales: Self Care (r=.193, p=.379), Cognitive Status (r=.318, p=.140), or Agitated Behaviors (r=-.040, p=.857).

Function (FAC Score) and presence of apathy (NPI-Apathy). Unlike significant correlations between function as measured by FAST score and all measures of apathy, relationships between function as measured by FAC subscale scores and measures of apathy varied widely (see Table 27). Function (FAC Cognitive Status subscale) significantly differed among persons exhibiting and not exhibiting apathy (NPI-Apathy) ($t(55) =-2.477$, p=.016). However, function (FAC Self Care subscale) did not significantly differ among persons exhibiting and not exhibiting apathy ($t(55) =-1.624$, p=.100). Function did not significantly differ by presence of apathy (NPI-Apathy) as measured by the remaining FAC subscales: Inappropriate Behavior ($t(55) =-.333$, p=.740) and Agitated Behavior ($t(55) =1.581$, p=.120).

Table 27. Mean Function (FAC Subscales) by Presence of Apathy (NPI-Apathy) [n=57]

	Exhibiting Apathy (NPI-Apathy) Mean ± SD	Not Exhibiting Apathy (NPI-Apathy) Mean ± SD
Self Care subscale	3.11 (.514)	2.85 (.656)
Inappropriate Behavior subscale	1.34 (.341)	1.30 (.477)
Cognitive Status subscale*	3.43 (.819)	2.82 (1.03)
Agitated Behaviors subscale	1.39 (.531)	1.64 (.616)

** Significant at the p=0.05 level (2-tailed)*
*** Significant at the p=0.01 level (2-tailed)*
FAC = Functional Abilities Checklist
NPI = Neuropsychiatric Inventory

Table 28. Mean Function (FAC Subscales) by Presence of Apathy (IA) [n=22]

	Exhibiting Apathy (IA) Mean ± SD	Not Exhibiting Apathy (IA) Mean ± SD
Self Care subscale*	2.96 (.641)	2.20 (.687)
Inappropriate Behavior subscale	1.29 (.346)	1.10 (.173)
Cognitive Status subscale*	2.96 (1.04)	1.80 (.885)
Agitated Behaviors subscale	1.60 (.548)	1.72 (.584)

** Significant at the p=0.05 level (2-tailed)*
*** Significant at the p=0.01 level (2-tailed)*
IA = Apathy Inventory
FAC = Functional Abilities Checklist

In summary, there was a significant relationship between function as measured by the FAC Cognitive Status subscale and the presence of apathy (NPI-Apathy, IA). The relationship between function as measured by the FAC Self Care and apathy (IA) was also significant. There was not a significant relationship between function (FAC Inappropriate Behaviors subscale) and presence of apathy (NPI-Apathy, IA). The relationships between the FAC Agitated Behavior subscale and the presence of apathy (NPI-Apathy) and the FAC Agitated Behavior subscale and apathy (IA) were not significant. Notice that persons exhibiting apathy were only *less*

functionally compromised than those not exhibiting apathy as measured by the FAC Agitated Behavior subscale, based on mean scores.

Function (FAC Score) and severity of apathy (NPI-Apathy). As depicted in Table 24, apathy severity (NPI-Apathy) was significantly correlated with function as measured by the FAC Self Care subscale (r=.325, p=.014) and function as measured by the FAC Agitated Behaviors subscale (r=-.324, p=.014). Apathy severity (NPI-Apathy) was also significantly correlated with function as measured by the FAC Cognitive status subscale (r=.448, p<.0001), but not with function as measured by the FAC Inappropriate Behavior subscale (r=.105, p=.435).

Function (FAC Score) and severity of apathy (IA). Apathy severity as measured by IA total score was significantly correlated with function as measured by the FAC Cognitive Status subscale (r=.449, p=.036) but not with function as measured by the remaining FAC Subscales: Self Care (r=.397, p=.067), Inappropriate Behavior (r=.229, p=.305), or Agitated Behavior (r=-.257, p=.278). The only significant correlation between apathy severity as measured by an IA subscale frequency x severity score and function as measured by an FAC subscale was between the IA Lack of Interest subscale frequency x severity score and function as measured by the FAC Cognitive Status subscale (r=.471, p=.027) (see bottom of Table 19).

To summarize, there was a significant relationship between function as measured by the FAC Cognitive Status subscale and apathy severity (NPI-Apathy, IA). The relationship between function as measured by the FAC Self Care subscale and apathy severity (NPI-Apathy) was significant, but the relationship between function as measured by the FAC Self Care subscale and apathy (IA) was not significant. There was not a significant correlation between function (FAC Inappropriate Behaviors subscale) and severity of apathy (NPI-Apathy, IA). Correlations between the FAC Agitated Behavior subscale and the severity of apathy (NPI-Apathy) were

significant, but correlations between the FAC Agitated Behavior subscale and apathy severity (IA) were not significant.

Relationships among measures of function. Both FAST and FAC data were available for the entire study sample (N=66). The FAC demonstrated good internal consistency (Cronbach's alpha=.818, n=28), based on the 28 individual items, and the majority of relationships among the four subscales demonstrated significance in this sample (see Table 29). Function as measured by FAST had a strong significant correlation with function as measured by both the FAC Self Care subscale (r=.681, p<.0001) and the FAC Cognitive Status subscale (r=.667, p<.0001)

Table 29. Relationships Among Measures of Function [N=66]

	FAC Self Care (p-value)	FAC Inapp. Behavior (p-value)	FAC Cognitive Status (p-value)	FAC Agitation (p-value)	FAST score (p-value)
FAC Self Care		.330 (.007)*	.759 (<.0001)**	.049 (.695)	.681 (<.0001)**
FAC Inapp. Behavior			.331 (.007)**	.402 (.001)**	.100 (.423)
FAC Cognitive Status				.021 (.870)	.667 (<.0001)**
FAC Agitation					-.228 (.066)

All values denote Pearson Correlation (Significance 2-tailed) unless otherwise specified
** Significant at the p=0.05 level (2-tailed)*
*** Significant at the p=0.01 level (2-tailed)*
FAC = Functional Abilities Checklist
FAST = Functional Assessment Staging Tool

Results By Specific Aim

Aim 1. Examine the extent to which individual characteristics (demographics and cognitive status) and social environment factors predict the severity of apathy in persons with AD, after adjusting for AD severity (based on FAST scale score) and APOE4 status.

The first step in analyzing Aim 1 was to identify individual characteristics and social environment factors associated with the presence and severity of apathy in persons with AD, prior to adjusting for AD severity and *APOE4* status.

Individual characteristic predictors of presence of apathy. The relationship between gender and presence of apathy (NPI-Apathy) was not statistically significant, X^2 (1, N = 57) =3.697, p=.055. A *t* test, with equal variances assumed, did not reveal a statistically significant difference in cognition (SIB total score) between persons who did not exhibit apathy (NPI-Apathy) (M=62.45, s=39.249) and who did exhibit apathy (NPI-Apathy) (M=45.17, s=37.936), *t*(55) =1.652, p=.104. There was a statistically significant difference in cognition (SIB total score) between persons who did not exhibit apathy (IA) (M=96.00, s=4.147) and who did exhibit apathy (IA) (M=69.63, s=30.311), *t*(16) =3.397, p=.004).

Individual characteristic predictors of severity of apathy. The relationship between age and apathy severity (NPI-Apathy) was not statistically significant (r=.211, p=.116). Apathy severity (NPI-Apathy) was significantly correlated with cognition (SIB total score) (r=-.380, p=.004). Participants who scored lower on the SIB, indicating more compromised cognitive function, were more likely to demonstrate more severe apathy as measured by the NPI-Apathy frequency x severity score. There was also a significant relationship between cognition (SIB total score) and apathy as measured by the IA total score (r=-.513, p=.015), IA Emotional Blunting subscale frequency x severity score (r=-.458, p=.032), IA Lack of Initiative subscale frequency x

severity score (r=-.433, p=.044) and IA Lack of Interest subscale frequency x severity score (r=-.504, p=.017). Persons with more compromised cognition as measured by SIB total score were more likely to display increased apathy severity as measured by the IA.

Modeling predictors of presence of apathy. NPI-Apathy data were used as the main Aim 1 outcome variable, as these data were more comprehensive than the IA data available for a subset of the sample (n=22). Analyses were completed, first using the NPI-Apathy binary variable as the dependent variable. Due to the categorical nature of the NPI-Apathy variable, logistic regression was selected.

In order to predict the presence of apathy (NPI-Apathy), hierarchical logistic regression, with gender and cognition (SIB total score) as the block one variables, and function (FAST total score) and number of *APOE4* alleles as block two variables was completed. The gender variable was classified as categorical. Number of *APOE4* alleles was treated as a quantitative variable, allowing for testing of additional risk of apathy for each additional copy of the rare *APOE4* allele. The resulting model did not significantly predict the presence of apathy (NPI-Apathy) (p=.056). Interestingly, though not significantly, for every one-point increase in FAST score, risk of apathy increased 1.26 times (95% CI: .902, 1.772, p=.173). Thus, a ten-point change in FAST score increases the risk of being apathetic approximately 10 (1.26^10) times (data not shown).

In order to more comprehensively predict the presence of apathy (NPI-Apathy), hierarchical logistic regression, with background factor variables [main demographic variables (age, gender) and cognition (SIB total score)] as block one variables, proximal factor variables [social environment as measured at time of data collection] as the block 2 variable, and function (FAST total score) and number of *APOE4* alleles as block three variables was completed. The gender and residence variables were classified as categorical. Number of *APOE4* alleles was

treated as a quantitative variable, allowing for testing of additional risk of apathy for each additional copy of the rare *APOE4* allele. The resulting model did not significantly predict the presence of apathy (NPI-Apathy), (p= .235) (data not shown).

Modeling predictors of severity of apathy. Multiple linear regression analyses were conducted with apathy severity, as measured by the NPI-Apathy frequency x severity score, as the outcome variable. Gender, age, and cognition (SIB total score) served as the initial individual characteristic predictors of apathy severity. In a hierarchical fashion, gender, age, and cognition (SIB total score) served as block one variables. FAST total score and number of *APOE4* alleles served as block two variables. Step 1 of the regression model examined the influence of background factors (gender, age, cognition [SIB total score]) as predictors of apathy severity (NPI-Apathy). As depicted in Table 30, age and cognition (SIB total score) were the only significant predictors of apathy severity (NPI-Apathy). Step 1 of the model, however, was significant, accounting for 20.5% of the variance in apathy severity (NPI-Apathy) (F=3.959, p=.014). Step 2 of the regression model examined the influence of background factors (gender, age, cognition [SIB total score]), while controlling for FAST total score and number of *APOE4* alleles, on apathy severity (NPI-Apathy). While none of the variables served as significant predictors of apathy severity on their own (NPI-Apathy), Step 2 of the model (see Table 30) significantly predicted 24.5% of the variance in apathy severity (NPI-Apathy) (F=2.860, p=.025), a modest (4%) increase in explained variance from Step 1.

Hierarchical multiple linear regression analyses were also carried out using more comprehensive individual characteristic predictors of apathy severity (NPI-Apathy), as proposed in Aim 1. Background factor variables [main demographic variables (age, gender) and cognition (SIB total score)] were block one variables. A Proximal factor variable [social environment as

measured by residence (collapsed dichotomized version) at time of data collection] was the block 2 variable, and function (FAST total score) and number of *APOE4* alleles served as block three variables. As depicted in Table 31, age and cognition (SIB total score) were the significant Step 1 (background factor) predictors of apathy severity (NPI-Apathy). Step 1 of the model was significant, accounting for 20.5% of the variance in apathy severity (NPI-Apathy) (F=3.959, p=.014). Step 2 of the regression model incorporated a proximal factor variable, social environment (residence at time of data collection). Age and cognition (SIB total score) remained the significant predictors of apathy severity (NPI-Apathy). Step 2 of the model was also significant, accounting for 20.8% of the variance in apathy severity (NPI-Apathy) (F=2.951, p=.030). Step 3 of the model used background factor variables and proximal factor variables, while controlling for function (FAST score) and *APOE4* status, to predict apathy severity (NPI-Apathy). No individual variables significantly predicted apathy severity (NPI-Apathy) in Step 3. However, the Step 3 model was significant; predicting 24.9% of the variance in apathy severity (NPI-Apathy) (F=2.370, p=.046).

Table 30. Gender, Age, and Cognition (SIB total score) as Predictors of Apathy Severity (NPI-Apathy) [n=50]

Predictors of Apathy Severity (NPI-Apathy)

Step	Variable	β	t	Tolerance
1				
	Gender	-2.67	-1.88	0.92
	Age (in years)	.252	2.14*	0.81
	Cognition (SIB total score, 0-100)	-.058	-3.18*	0.80
	Model $R^{2 =}$ 0.205			
	F of $R^{2 =}$ 3.959, p=.014*			
2				
	Gender	-2.57	-1.81	0.91
	Age (in years)	.249	1.97	0.70
	Cognition (SIB total score, 0-100)	-.038	-1.58	0.46
	Function (FAST score)	.458	1.43	0.55
	APOE4	-.061	-.054	0.69
	Model $R^{2 =}$ 0.245			
	F of $R^{2 =}$ 2.86, p=.025*			
	Note. *p< 0.05			

FAST = Functional Assessment Staging Tool
NPI = Neuropsychiatric Inventory
SIB = Severe Impairment Battery

Table 31. Comprehensive Predictors of Apathy Severity (NPI-Apathy) [n=50]

Comprehensive Predictors of Apathy Severity (NPI-Apathy)

Step	Variable	β	t	Tolerance
1				
	Gender	-2.67	-1.88	0.92
	Age (in years)	.252	2.14*	0.81
	Cognition (SIB total score, 0-100)	-.058	-3.18*	0.80
	Model $R^{2 =}$ 0.205			
	F of $R^{2 =}$ 3.959, p=.014*			
2				
	Gender	-2.65	-1.85	0.92
	Age (in years)	.261	2.15*	0.78
	Cognition (SIB total score, 0-100)	-.059	-3.16*	0.80
	Social Environment (Residence)	.524	.380	0.96
	Model $R^{2 =}$ 0.208			
	F of $R^{2 =}$ 2.95, p=.030*			
	Note. *p< 0.05			
3	Gender	-2.54	-1.78	0.91
	Age (in years)	.255	1.99	0.69
	Cognition (SIB total score, 0-100)	-.039	-1.60	0.45
	Social Environment (Residence)	.598	.430	0.93
	Function (FAST score)	.454	1.41	0.55
	APOE4	-.140	-.121	0.67
	Model $R^{2 =}$ 0.249			
	F of $R^{2 =}$ 2.37, p=.046*			

FAST = Functional Assessment Staging Tool
NPI = Neuropsychiatric Inventory
SIB = Severe Impairment Battery

In summary, binary logistic regression did not produce a significant model able to predict presence of apathy as measured by the NPI-Apathy. However, as depicted in Tables 30 and 31, both linear regression models (Model 1 and Model 2) were able to significantly predict apathy severity (NPI-Apathy). To that end, all steps of each regression model were significant predictors of apathy severity (p=.014-.046). However, few variables individually predicted apathy severity (NPI-Apathy), aside from age and cognition (SIB total score) in initial steps of both models. Model 1 (see Table 30) significantly predicted 24.5% of the variance in apathy severity (NPI-Apathy) (F=2.860, p=.025), based on five predictor variables: Gender, age, cognition (SIB total score,) function (FAST score), and *APOE4* genotype status. Model 2 (see Table 31) significantly predicted 24.9% of the variance in apathy severity (NPI-Apathy) (F=2.370, p=.046), based on six predictor variables. Therefore, the inclusion of social environment as measured by place of residence at time of data collection (dichotomized variable), only predicted an additional 0.04% of the variance in apathy severity (NPI-Apathy). Background factor variables [main demographic variables (age, gender) and cognition (SIB total score)], function (FAST total score), and number of *APOE4* alleles served as the most significant predictors of apathy severity (NPI-Apathy). The resulting final best model was then: Apathy severity (NPI-Apathy) = -9.421(Constant) - 2.57(gender) + .249(age) - .038(cognition) + .458(function) - .061(*APOE4*) + $\sum B_j X_j$ (where X_j = other covariates).

Aim 2. Examine the extent to which variations in the *Oxytocin Receptor (OXTR*) gene are associated with apathy in persons with AD. For Aim 2 analyses, variables related to *OXTR* included a variable based on genotype for each of the five SNPs. Number of *OXTR* alleles was treated as a quantitative variable, allowing for testing of additional risk of apathy for each additional copy of the rare *OXTR* allele. Relationships were examined between all measures of

apathy prevalence (NPI-Apathy binary variable, IA binary variable) and apathy severity (NPI-Apathy frequency x severity score, IA total score and frequency x severity scores for each of the IA subscales), and genotype status for each of five *OXTR* SNPs.

Relationships between OXTR SNPs and presence of apathy.

Relationships between OXTR SNPs and presence of apathy (NPI-Apathy). No significant relationships emerged between presence of apathy (NPI-Apathy) and genotype status for each of five *OXTR* SNPs. A *t* test, with equal variances assumed, failed to reveal a statistically significant difference in number of *OXTR1* alleles for persons exhibiting apathy (NPI-Apathy) and those not exhibiting apathy (NPI-Apathy) ($t(51) = -.619$, $p = .538$). A *t* test, with equal variances assumed, also failed to reveal a statistically significant difference in number of *OXTR2* alleles for persons exhibiting apathy (NPI-Apathy) and those not exhibiting apathy (NPI-Apathy) ($t(49) = .962$, $p = .341$). There was no significant difference in number of *OXTR3* alleles for persons exhibiting apathy (NPI-Apathy) and those not exhibiting apathy (NPI-Apathy) ($t(53) = -.485$, $p = .629$). There was also no significant difference in number of *OXTR4* alleles for persons exhibiting apathy (NPI-Apathy) and those not exhibiting apathy (NPI-Apathy) ($t(53) = -.283$, $p = .779$). Finally, there was no significant difference in number of *OXTR5* alleles for persons exhibiting apathy (NPI-Apathy) and those not exhibiting apathy (NPI-Apathy) ($t(53) = -.485$, $p = .629$).

Relationships between OXTR SNPs and presence of apathy (IA). Relationships between *OXTR* SNPs and presence of apathy (IA) were also examined using independent samples *t* tests. Similarly, no significant relationships emerged between presence of apathy (IA) and genotype status for each of five *OXTR* SNPs (data not shown).

Modeling relationships between OXTR SNPs and presence of apathy. NPI-Apathy data were used as the main Aim 2 outcome variable, as these data were more comprehensive than the IA data available for a subset of the sample (n=22). Five binary logistic regression analyses were run, with presence of apathy (NPI-Apathy) as the dependent variable and cognition (SIB total score), *APOE4* genotype status, and each of the *OXTR* SNPs as covariates. Number of *OXTR* alleles was treated as a quantitative variable in each of the five analyses, allowing for testing of additional risk of apathy as measured by NPI-Apathy for each additional copy of the rare *OXTR* allele. The resulting models did not significantly predict presence of apathy as measured by the NPI-Apathy binary variable (data not shown).

Relationships between OXTR SNPs and severity of apathy (NPI-Apathy). One-way ANOVA was utilized to compare mean apathy severity scores (NPI-Apathy) across the three genotypes for each *OXTR* SNP (see Tables 32-36). There were no significant relationships, though a relationship emerged between apathy severity (NPI-Apathy) and *OXTR2* (rs53576) (F=2.747 (df=2), p=.076). Persons with the AA genotype were more likely, though not significantly, to display more severe apathy as measured by the NPI-Apathy.

Relationships between OXTR SNPs and severity of apathy (IA). One-way ANOVA was utilized to compare mean apathy severity scores (NPI-Apathy) across the three genotypes for each *OXTR* SNP (see Tables 32-36). A significant relationship emerged between apathy severity (IA) and *OXTR2* (rs53576) (F= 3.696 (df=2), p=.045). Persons with the AA genotype were more likely to display more severe apathy. However, interpretation of these results must be reserved with caution, given that only one individual with IA data available possessed the AA genotype. Correlations between *OXTR* alleles and all apathy measures were also analyzed (see Table 37).

Table 32. Apathy Severity by *OXTR1* (rs237885) Genotype

	OXTR1 (rs237885) Genotype		
	CC [n = 20]	CT [n = 27]	TT [n = 6]
Apathy Severity (NPI-Apathy) Mean ± SD	4.95 (5.19)	4.56 (4.70)	5.33 (5.47)
F= .076 (df=2), p=.927			
	CC [n = 8]	CT [n = 11]	TT [n = 2]
Apathy Severity (IA) Mean ± SD	12.75 (10.26)	9.64 (13.25)	18.00 (25.12)
F= .386 (df=2), p=.685			

NPI = Neuropsychiatric Inventory FxS= Frequency by Severity
IA = Apathy Inventory

Table 33. Apathy Severity by *OXTR2* (rs53576) Genotype

	OXTR2 (rs53576) Genotype		
	GG [n = 25]	AG [n = 23]	AA [n = 3]
Apathy Severity (NPI-Apathy) Mean ± SD	5.64 (4.77)	3.00 (4.33)	8.00 (6.93)
F=2.747 (df=2), p=.076			
	GG [n = 9]	AG [n = 11]	AA [n = 1]
Apathy Severity (IA) Mean ± SD	14.89 (11.55)	6.73 (11.21)	36.00
F= 3.696 (df=2), p=.045			

NPI = Neuropsychiatric Inventory FxS= Frequency by Severity
IA = Apathy Inventory

Table 34. Apathy Severity by *OXTR3* (rs237885) Genotype

	OXTR3 (rs237885) Genotype		
	GG [n = 10]	GT [n = 32]	TT [n = 13]
Apathy Severity (NPI-Apathy) Mean ± SD	3.70 (3.59)	4.78 (5.08)	6.48 (5.30)
F=.958 (df=2), p=.390			
	GG [n = 3]	GT [n = 15]	TT [n = 3]
Apathy Severity (IA) Mean ± SD	13.00 (13.08)	11.27 (12.14)	12.00 (20.79)
F= .022 (df=2), p=.978			

NPI = Neuropsychiatric Inventory FxS= Frequency by Severity
IA = Apathy Inventory

Table 35. Apathy Severity by *OXTR4* (rs6770632) Genotype

	OXTR4 (rs6770632) Genotype		
	CC [n = 39]	AC [n = 12]	AA [n = 4]
Apathy Severity (NPI-Apathy) Mean ± SD	4.90 (4.75)	4.33 (5.78)	7.75 (3.69)
F=.741(df=2), p=.482			
	CC [n = 20]	AC [n = 1]	AA [n = 0]
Apathy Severity (IA) Mean ± SD	11.30 (13.05)	18.00	x
F= .251 (df=2), p=.622			

NPI = Neuropsychiatric Inventory FxS= Frequency by Severity
IA = Apathy Inventory

Table 36. Apathy Severity by *OXTR5* (rs2268491) Genotype

	OXTR5 (rs2268491) Genotype		
	CC [n = 40]	CT [n = 13]	TT [n = 2]
Apathy Severity (NPI-Apathy) Mean ± SD	5.05 (4.91)	4.92 (5.20)	4.00 (5.66)
F=.043 (df=2), p=.958			
	CC [n = 15]	CT [n = 5]	TT [n = 1]
Apathy Severity (IA) Mean ± SD	9.33 (11.82)	20.80 (13.08)	0.00
F= 2.16 (df=2), p=.144			

NPI = Neuropsychiatric Inventory FxS= Frequency by Severity
IA = Apathy Inventory

Table 37. Correlations between Apathy Severity and *OXTR* Genotype in Persons with AD

	NPI-Apathy FxS Score (p-value)	IA Total Score (p-value)	IA Emotional Blunting FxS (p-value)	IA Lack of Initiative FxS (p-value)	IA Lack of Interest FxS (p-value)
OXTR1	.001 (.997)	.023 (.923)	.076 (.743)	-.032 (.889)	.028 (.904)
OXTR2	-.109 (.447)	-.033 (.886)	.064 (.783)	-.091 (.677)	-.042 (.855)
OXTR3	.186 (.174)	-.021 (.927)	.086 (.710)	-.142 (.539)	.019 (.934)
OXTR4	.088 (.525)	.114 (.622)	.134 (.562)	-.185 (.423)	.387 (.083)
OXTR5	-.033 (.812)	.153 (.507)	.068 (.769)	.253 (.269)	.079 (.735)

** Significant at the p=0.05 level (2-tailed)*
*** Significant at the p=0.01 level (2-tailed)*
NPI = Neuropsychiatric Inventory
IA = Apathy Inventory
FxS= Frequency by Severity

Modeling relationships between OXTR SNPs and severity of apathy (NPI-Apathy).

Regression models were calculated to examine the influence of each of five *OXTR* SNPS, controlling for cognition (SIB total score) and number of *APOE4* alleles, on apathy severity (NPI-Apathy). This approach resulted in the creation of five separate models. One of five models significantly predicted apathy severity (NPI-Apathy). As depicted in Table 38, *OXTR2 (*rs53576) genotype, cognition (SIB total score) and number of *APOE4* alleles were significant predictors of

apathy severity (NPI-Apathy). *OXTR2* genotype, cognition (SIB total score), and number of *APOE4* alleles significantly predicted 19.4% of the variance in apathy severity (NPI-Apathy) (F=3.379, p=.027), with the AA genotype associated with more severe apathy. *OXTR2* (rs53576) genotype was significantly associated with apathy severity as measured by the IA (F= 3.696 (df=2), p= .045). Again, with the AA genotype associated with more severe apathy.

Table 38. *OXTR2 (*rs53576), Cognition (SIB total score), and *APOE4* as Predictors of Apathy Severity (NPI-Apathy) [n=46]

Predictors of Apathy Severity (NPI-Apathy)

Variable	β	t	Tolerance
*OXTR2 (*rs53576)	-1.47	-1.37	0.96
Cognition (SIB total score, 0-100)	-.055	-2.92*	0.81
APOE4	-2.52	-2.17*	0.82
Model $R^{2=}$ 0.194			
F of $R^{2=}$ 3.379, p=.027			

NPI = Neuropsychiatric Inventory
SIB = Severe Impairment Battery

Table 39. *OXTR3* (rs237885), Cognition (SIB total score) and *APOE4* as Predictors of Apathy Severity (NPI-Apathy) [n=50]

Predictors of Apathy Severity (NPI-Apathy)

Variable	β	t	Tolerance
OXTR3 (rs237885)	1.09	1.12	0.98
Cognition (SIB total score, 0-100)	-.042	-2.26*	0.86
APOE4	-.973	-.927	0.86
Model $R^{2=}$ 0.136			
F of $R^{2=}$ 2.414, p=.079			

NPI = Neuropsychiatric Inventory
SIB = Severe Impairment Battery

As depicted in Table 39, *OXTR3* genotype, controlling for cognition (SIB total score) and number of *APOE4* alleles, was not a significant predictor of apathy severity (NPI-Apathy). *OXTR3* (rs237885) genotype, cognition (SIB total score), and number of *APOE4* alleles predicted 13.6% of the variance in apathy severity (NPI-Apathy) (F=2.414, p=.079), though this did not reach statistical significance.

In summary, a single variation in *OXTR* is significantly associated with apathy in persons with AD. *OXTR2* genotype, cognition (SIB total score), and number of *APOE4* alleles significantly predicted 19.4% of the variance in apathy severity (NPI-Apathy) (F=3.379, p=.027), with the AA genotype associated with more severe apathy. *OXTR3* (rs237885) genotype, cognition (SIB total score), and number of *APOE4* alleles predicted 13.6% of the variance in apathy severity (NPI-Apathy) (F=2.414, p=.079), not reaching significance but possibly warranting further exploration.

Aim 3. Examine the extent to which severity of apathy influences functional status in persons with AD, after adjusting for AD severity. Function as measured by FAST score and function as measured by each of the FAC subscales were used as Aim 3 outcome variables. NPI-Apathy data were used as the main Aim 3 independent variable, as these data were more comprehensive than the IA data available for a subset of the sample (n=22). In order to control for AD severity, SIB total score was added to each of the models in Aim 3 multiple linear regression analyses. Initial calculations, as previously presented, revealed significant relationships between apathy and functional status in persons with AD (see Tables 24, 25, 28).

Relationships between function and presence of apathy. Function (FAST score) significantly differed among persons exhibiting apathy and not exhibiting apathy as measured by both the NPI-Apathy and the IA. Function as measured by the FAC Cognitive Status subscale

was significantly related to the presence of apathy (NPI-Apathy), though there were not significant relationships between presence of apathy (NPI-Apathy) and the three remaining subscales. Function as measured by the FAC Self Care and FAC Cognitive Status subscales was significantly related to the presence of apathy (IA), but there were not significant relationships between presence of apathy (IA) and the two remaining subscales.

Relationships between function and severity of apathy. Function as measured by FAST score was significantly correlated with apathy severity. Significant relationships were also identified between apathy severity and function (FAST score) across all three apathy domains of the IA. Apathy severity (NPI-Apathy) was significantly correlated with function as measured by three FAC subscales: Self Care, Cognitive Status, Agitated Behaviors, but not with function as measured by the FAC Inappropriate behaviors subscale. Apathy severity (IA) was significantly correlated with function as measured by the FAC Cognitive Status subscale, but not with the three remaining subscales.

Presence of apathy and functional status.

Modeling relationships between presence of apathy and functional status (FAST score). Multiple linear regression was used to examine the influence of presence of apathy (NPI-Apathy), controlling for cognition (SIB total score), on function (FAST score). As depicted in Table 40, both presence of apathy (NPI-Apathy) and cognition (SIB total score) were significant predictors of function (FAST score). Presence of apathy (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted 51.4% of the variance in function as measured by FAST score ($F=28.587$, $p<.0001$).

Table 40. Presence of Apathy (NPI-Apathy) and Cognition (SIB total score) as Predictors of Function (FAST score) [n=57]

Predictors of Function (FAST score)

Variable	β	t	Tolerance
Presence of Apathy (NPI-Apathy)	1.47	2.38*	0.95
Cognition (SIB total score, 0-100)	-.050	-6.49*	0.95
Model R^2 = 0.514			
F of R^2 = 28.587, p <.0001			

FAST = Functional Assessment Staging Tool
NPI = Neuropsychiatric Inventory
SIB = Severe Impairment Battery

Modeling relationships among presence of apathy and functional status (FAC subscales). Multiple linear regression analyses were also used to examine whether the presence of apathy (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted function as measured by each of the FAC subscales. As depicted in Table 41, presence of apathy (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted 25.5% of the variance in function as measured by the FAC Self Care subscale (F=9.523, p<.0001). Presence of apathy (NPI-Apathy), controlling for cognition (SIB total score), did not significantly predict function as measured by the FAC Inappropriate Behaviors subscale (F=1.427, p=.249, R-Square=.050). As depicted in Table 42, presence of apathy (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted 47.5% of the variance in function as measured by the FAC Cognitive Status subscale (F=24.409, p<.0001). Finally, presence of apathy (NPI-Apathy), controlling for cognition (SIB total score), did not significantly predict function as measured by the FAC Agitated Behaviors subscale (F=1.798, p=.175, R-Squared=.062).

Table 41. Presence of Apathy (NPI-Apathy) and Cognition (SIB total score) as Predictors of Function (FAC Self Care subscale) [n=57]

Predictors of Function (FAC Self Care subscale)

Variable	β	t	Tolerance
Presence of Apathy (NPI-Apathy)	.133	.931	0.95
Cognition (SIB total score, 0-100)	-.007	-3.90*	0.95
Model $R^{2 =}$ 0.255			
F of $R^{2 =}$ 9.253, p <.0001			

FAC = Functional Abilities Checklist
NPI = Neuropsychiatric Inventory
SIB = Severe Impairment Battery

Table 42. Presence of Apathy (NPI-Apathy) and Cognition (SIB total score) as Predictors of Function (FAC Cognitive Status subscale) [n=57]

Predictors of Function (FAC Cognitive Status subscale)

Variable	β	t	Tolerance
Presence of Apathy (NPI-Apathy)	.348	1.79	0.95
Cognition (SIB total score, 0-100)	-.015	-6.21*	0.95
Model $R^{2 =}$ 0.475			
F of $R^{2 =}$ 24.409, p <.0001			

FAC = Functional Abilities Checklist
NPI = Neuropsychiatric Inventory
SIB = Severe Impairment Battery

Severity of apathy and functional status.

Severity of apathy and functional status (FAST score). Multiple linear regression analyses were used to examine whether apathy severity (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted function (FAST score). As depicted in Table 43, both severity of apathy (NPI-Apathy) and cognition (SIB total score) were significant predictors of function

(FAST score). Severity of apathy (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted 50.7% of the variance in function as measured by FAST score (F=27.774, p<.0001).

Table 43. Severity of Apathy (NPI-Apathy) and Cognition (SIB total score) as Predictors of Function (FAST score) [n=57]

Predictors of Function (FAST score)

Variable	β	t	Tolerance
Severity of Apathy (NPI-Apathy)	.143	2.19*	0.86
Cognition (SIB total score, 0-100)	-.048	-5.76*	0.86
Model R^2 = 0.507			
F of R^2 = 27.774, p < .0001			

FAST = Functional Assessment Staging Tool
NPI = Neuropsychiatric Inventory
SIB = Severe Impairment Battery

Severity of apathy and functional status (FAC subscales). Multiple linear regression was also used to examine whether apathy severity (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted function as measured by each of the FAC subscales. As depicted in Table 44, apathy severity (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted 26.6% of the variance in function as measured by the FAC Self Care subscale (F=2.513, p<.0001). Apathy severity (NPI-Apathy) controlling for cognition (SIB total score), did not significantly predict function as measured by the FAC Inappropriate Behaviors subscale (F=1.441, p=.246, R-Square=.051). As depicted in Table 45, apathy severity (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted 48.8% of the variance in function as measured by the FAC Cognitive Status subscale (F=25.766, p<.0001). Finally, apathy severity (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted

10.9% of the variance in function as measured by the FAC Agitated Behaviors subscale (F=3.301, p=.044) (see Table 46).

Table 44. Severity of Apathy (NPI-Apathy) and Cognition (SIB total score) as Predictors of Function (FAC Self Care subscale) [n=57]

Predictors of Function (FAC Self Care subscale)

Variable	β	t	Tolerance
Severity of Apathy (NPI-Apathy)	.019	1.28	0.86
Cognition (SIB total score, 0-100)	-.006	-3.43*	0.86
Model R^2 = 0.266			
F of R^2 = 9.761, p <.0001			

FAST = Functional Assessment Staging Tool
NPI = Neuropsychiatric Inventory
SIB = Severe Impairment Battery

Table 45. Severity of Apathy (NPI-Apathy) and Cognition (SIB total score) as Predictors of Function (FAC Cognitive Status subscale) [n=57]

Predictors of Function (FAC Cognitive Status subscale)

Variable	β	t	Tolerance
Severity of Apathy (NPI-Apathy)	.044	2.17*	0.86
Cognition (SIB total score, 0-100)	-.014	-5.51*	0.96
Model R^2 = 0.488			
F of R^2 = 25.766, p < .0001			

FAST = Functional Assessment Staging Tool
NPI = Neuropsychiatric Inventory
SIB = Severe Impairment Battery

Table 46. Severity of Apathy (NPI-Apathy) and Cognition (SIB total score) as Predictors of Function (FAC Agitated Behaviors subscale) [n=57]

Predictors of Function (FAC Agitated Behaviors subscale)

Variable	β	t	Tolerance
Severity of Apathy (NPI-Apathy)	-.035	-2.15*	0.86
Cognition (SIB total score, 0-100)	.001	.477	0.86
Model R^2 = 0.109			
F of R^2 = 3.301, p=.044			

FAST = Functional Assessment Staging Tool
NPI = Neuropsychiatric Inventory
SIB = Severe Impairment Battery

In summary, severity of apathy significantly influences functional status in persons with AD, after controlling for AD severity. Both presence of apathy and apathy severity predicted overall function as measured by the FAST scale, controlling for cognitive status. Further, apathy severity as measured by NPI-Apathy frequency x severity score, controlling for cognition as measured by SIB total score, significantly predicted self-care, cognitive and selected behavioral aspects of function. Presence of apathy as measured by the NPI-Apathy, controlling for cognition as measured by SIB total score, significantly predicted self-care and cognitive aspects of function, rather than behavioral aspects.

Results Summary

These analyses produced several meaningful results. First, study results indicated important observations about the prevalence and characteristics of apathy in persons with AD. For example, men experienced a higher prevalence and severity of apathy than women in this sample. Additionally, a strong relationship emerged between apathy and cognition, with poorer cognitive status associated with more severe apathy. Consistent with the NDB model, a

combination of background factor variables [main demographic variables (age, gender) and cognition (SIB total score)], function (FAST total score), and number of *APOE4* alleles served as the most significant predictors of apathy, predicting 24.5% of the variance in apathy severity (NPI-Apathy) (F=2.370, p=.046). The IA instrument proved a useful measurement tool for apathy, demonstrating reliability for examining cognitive, behavioral and emotional domains of apathy in persons with AD as well as concurrent validity with the highly accepted NPI-Apathy.

Second, this study revealed a novel association between DNA variations in *OXTR* with apathy in persons with AD. A trend emerged between apathy severity (NPI-Apathy) and *OXTR2* (rs53576) (F= 2.747 (df=2), p= .076), where persons with the AA genotype were more likely to display more severe apathy. Further, *OXTR2* genotype, in combination with cognition (SIB total score) and number of *APOE4* alleles, significantly predicted 19.4% of the variance in apathy severity (NPI-Apathy) (F=3.379, p=.027), with the AA genotype associated with more severe apathy. A trend emerged with the *OXTR3* (rs237885) variant, with *OXTR3* (rs237885) genotype, cognition (SIB total score), and number of *APOE4* alleles predicting 13.6% of the variance in apathy severity (NPI-Apathy) (F=2.414, p=.079), though the relationship did not reach significance.

Finally, both presence of apathy and apathy severity, when controlling for cognitive status, predicted overall function as measured by FAST scale score as well as multiple subdomains of function as measured by the FAC. Presence of apathy (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted self-care and cognitive aspects of function, rather than behavioral aspects. Apathy severity (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted self-care, cognitive and selected behavioral aspects of function.

CHAPTER 6: DISCUSSION

Despite the high prevalence and negative sequela associated with apathy, little is known about characteristics of persons with Alzheimer Disease (AD), including biologic factors that contribute to the presence and severity of apathy in persons with AD. The knowledge gap prevents healthcare providers from properly identifying which individuals might be more prone to apathy, and identifying how resident characteristics and social environmental factors impact the presence and severity of apathy in persons with AD as well as subsequent functional outcomes.

This cross-sectional descriptive study was designed to examine the extent to which resident characteristics and social environment factors predict the severity of apathy in persons with AD, after adjusting for AD severity. Because oxytocin (OT) was recently implicated as a moderator of human social behaviors with possible significance to social decision-making (Averbeck, 2010; Campbell, 2010), the *Oxytocin Receptor* (*OXTR)* gene was examined as an important potential modifier in the prediction of apathy in persons with AD. The effect of apathy on functional status among this sample was investigated, as supporting evidence exists for the deleterious effect of apathy on functional status in persons with dementia (Lam et al., 2008).

Key Findings Related to Sample Characteristics

Demographic Characteristics. The majority of study participants (98.5%, n=65) were over age 60, which is consistent with data from the National Institute on Aging (2013), suggesting that the vast majority of AD cases are late-onset in nature. AD and other dementias are most common among females (Alzheimer's Association, 2012), with females appropriately making up the majority of the study sample (69.7%, n=46).

Genotype/Genetic Measurement. This study examined genotype as background factor variables impacting apathy and function in persons with dementia. Genetic analyses in this study included two *Apolipoprotein E (APOE*) SNPs (rs429358, rs7412) used to determine *Apolipoprotein E-4 (APOE4)* status and five *OXTR* gene SNPs (rs237885, rs53576, rs237895, rs6770632, rs2268491).

***Apolipoprotein E (APOE*).** The literature states that about 40% of all people who develop late-onset AD are carriers of the *APOE4* allele (National Institute on Aging, 2013). Frequencies in this study were consistent with the literature, with 31% (n=36) of participants as carriers of the *APOE4* allele based on genotype data. Among this sample, the number of *APOE4* alleles and age at symptom onset were highly significant correlated at -.486 ($p<.0001$). Persons with more copies of the *APOE4* allele were significantly younger at the time of symptom onset. This is consistent with seminal work by Corder and colleagues (1993), which demonstrated that each additional *APOE4* allele shifted onset to a younger age (Corder et al., 1993). Individual risk for AD would be expected to increase significantly for each additional *APOE4* allele (Corder et al., 1993), though there was not a significant difference in number of *APOE4* alleles for persons with and without a formal AD diagnosis in this study ($t(51) =-.885$, $p=.380$). A formal diagnosis of AD was made for 60.6% (n=40) of the sample, based on family report and chart review. This may suggest lack of consistent AD diagnosis among study participants. For this reason, a number of strategies were used in these analyses to control for AD status and severity, including *APOE4* genotype status, FAST score, or SIB total score.

The rationale for controlling for AD status and severity in this dissertation study is supported by the literature, as symptom variability occurs throughout the disease. Common clinical features of AD include confusion, poor judgment, language disturbance, agitation,

withdrawal, and hallucinations (Bird, 2010). In addition to symptom variability, clinical practice related to diagnosis of AD varies substantially.

Cognitive decline may be evaluated with the use of neuroimaging studies such as magnetic resonance imaging (MRI) or computed tomography (CT), single photon emission computerized tomography (SPECT), or positron emission tomography (PET), by potentially detecting neurological damage due to atrophy of specific areas of the brain (Aderinwale et al., 2010; Bird, 2010). However, these methods may not be effective for evaluation and diagnosis in the early stages of cognitive decline. Genetics also play a role in the risk for AD (Corder et al., 1993; Pericak-Vance et al., 1991), with the emerging use of biomarkers for early diagnosis of AD. However, genetic analysis for AD is often limited to research settings (Aderinwale, et al. 2010) and is not currently recommended for the population at large, due to the inability to predict individual risk and the lack of disease treatment options. Additionally, *APOE4* is the only undisputed risk allele for late-onset AD (Corder et al., 1993).

Cognitive decline may also be evaluated with the use of tools like the Mini-Mental State Examination (MMSE), the Severe Impairment Battery (SIB), or the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), common in clinical and research settings (Aderinwale et al., 2010). However, the line between normal cognitive decline and pathological cognitive decline is unclear due to the inherent subtleties in differentiation between what is "normal," "pathological," and "mildly pathological" from person to person. Even in the 21st century, autopsy remains the gold standard for diagnosis of AD (Aderinwale et al., 2010).

Despite the diagnostic challenges related to AD, it is important to note that study participants with and without a formal AD diagnosis did not exhibit differences in phenotype. Those with a formal AD diagnosis, based on family report or chart review, did not demonstrate

differential cognition (SIB total score) compared to those without a formal AD diagnosis in this study. There was also no difference in prevalence or severity of apathy among study participants with and without a formal diagnosis of AD. It may be that the study participants lacking a formal AD diagnosis were under-diagnosed or had not undergone conclusive diagnostic studies.

***Oxytocin Receptor (OXTR)* gene.** DNA variants across the candidate *OXTR* gene provided a useful mechanism to test an association between OT and apathy. *OXTR* genotype frequencies did not differ by gender, and a lack of ethnic diversity prevented adequate examination of the relationship between *OXTR* genotypes and ethnicity. These observations are consistent with other research. For example, *OXTR2* (rs53576), a main *OXTR* variant of interest in this study, did not demonstrate genotype-by-sex (X^2 (2) =1.32, p=.52) or genotype-by-ethnicity (X^2 (6) =7.22, p=.30) differences in a recent longitudinal study examining the relationship between *OXTR* and prosocial behavior among individuals enduring stressful life events and physical ailments (Poulin & Holman, 2013), nor in a study examining the relationship between OXTR rs53576 and environmental stress (Lucas-Thompon & Holman, 2013).

Cognitive Abilities. Pathological and progressive cognitive decline is a hallmark finding in AD, with an average duration of eight to ten years, but ranging from one to twenty-five years (Bird, 2010). Participants in this study reported a wide range in time since onset of symptoms (1-23 years), with a mean time since onset of 8.39 (SD=5.02) years, consistent with published reports of AD duration. Cognitive decline involves worsened performance in one or several cognitive domains such as memory, orientation, language, executive function or praxis, beyond what might be expected for the person's age and educational level (Plassman et al., 2010). The cognitive characteristics of this sample suggested moderate impairment, as evidence by a mean

total SIB score of 50.66 (SD=39.09; range=0-100). However, the level of cognitive impairment varied widely, despite the fact that the vast majority of participants were institutionalized.

Social Environment. Social environment proved to be a particular measurement challenge. The primary measure of social environment in this study was based on residence at the time of data collection, providing a gross measurement of the social aspects of an environment based on designation as dementia-specific. The Ambiance Scale (AS) provided a potentially more refined measure of social environment, but was only available for a small subset of participants, limiting its usefulness in subsequent analyses. Interestingly, social environment as measured by residence at time of data collection and social environment as measured by AS total score were not significantly correlated (r=-.330, p=.124). This finding may suggest that these measures of social environment are not capturing the same aspects of the social environment. Additionally, associations between social environment and other key study variables were largely lacking in this study. The two variables used to measured social environment may not have adequately captured the aspects of social environment relevant to apathy.

Behavioral Symptoms. Common behavioral symptoms in AD include sleeplessness, agitation, wandering, anxiety, apathy, anger and depression (Lyketsos et al., 2002; Mega et al., 1996; National Institute on Aging, 2013). These and other personality changes and behavioral symptoms may cause a person to seek clinical evaluation for AD or may emerge over the course of the disease (Petry et al., 1988). In this study, 93% of persons for whom Neuropsychiatric Inventory (NPI) data were available (n=57) exhibited at least one behavioral symptom. Prevalence of behavioral symptoms among study participants is in excess of the 75% reported

for participants with dementia as part of the Cardiovascular Healthy Study (Lyketsos et al., 2002) and the 72% reported among individuals with AD using the NPI (Mega et al., 1996).

The prevalence of specific types of behavioral symptoms in this study was relatively consistent with the literature. The most frequent behavioral disturbances reported among persons with dementia have been apathy, depression, and agitation/aggression (Lyketsos et al., 2002), apathy (Mega et al., 1996), or agitation and aggression (Cohen-Mansfield, 1996). In this sample, apathy (n=35, 53.0%), agitation/aggression (n=35, 53.0%), and irritability/lability (n=31, 470%) were the most frequently exhibited behavioral symptoms among study participants, as measured by the NPI. While a comprehensive analysis of behavioral symptoms among persons with AD was not the focus of this dissertation study, correlations between apathy and depression were briefly examined based on evidence that apathy is distinct from depression, though the two may be difficult to distinguish (Lerner et al., 2007). Additional supporting evidence included the exploration of apathy and depression in relationship to functional status or disability (Benoit et al., 2008; Lam et al., 2008). Depression, as measured by the NPI Depression subscale (NPI-Depression) was not significantly correlated with apathy in this study.

Apathy. For the purpose of this dissertation research, apathy was defined as a disorder of motivation with deficits in behavioral, emotional, and/or cognitive domains. Prevalence of apathy ranged from 53.0% (n=35) as measured by the NPI-Apathy and 71.4% (n=15) as measured by the Apathy Inventory (IA) among a subset of the sample. Comparatively, the literature suggests that apathy occurs in over 90% of persons with AD across the disease trajectory with varying severity (Benoit et al., 2008; Mega et al., 1996). Conservative estimates suggest apathy prevalence closer to 30% (Lyketsos et al., 2002, Mega et al., 1996).

The wide range of apathy prevalence in the literature may be contributed to the wide variety of measures of apathy utilized by researchers. For example, Dykstra Goris (manuscript in development) performed an integrated literature review including 15 studies focused on nonpharmacologic interventions for reducing apathy in persons with dementia. Measures of apathy varied widely, and both paper and pencil and observational measures were utilized. English language measures included the Dementia Apathy Interview and Rating (DAIR) Scale (Ferrero-Arias et al., 2011), the Passivity in Dementia Scale (PDS) (Kolanowski et al., 2011), and the Dementia Behavior Disturbance Scale (Hattori et al., 2011)), among others. The Neuropsychiatric Inventory (NPI) was most often utilized to measure apathy among included studies (Ferrero-Arias et al., 2011; Fischer-Terworth & Probst, 2011; Lam et al., 2010; Niu et al., 2010; Politis et al., 2004; Raglio et al., 2010; Raglio et al., 2008). Selected studies used additional observational measures such as apathy ratings based on video recordings (Raglio et al., 2010; Raglio et al., 2008; van Weert et al., 2005).

To that end, the lack of a clear conceptual definition of apathy in the literature may be to blame for the limited number of high-quality tools available for apathy operationalization. Clinically, apathy is mentioned in association with schizophrenia, delirium, dementia due to Human Immunodeficiency Virus (HIV), dementia due to head trauma, dementia due to Pick's disease, amnestic disorder due to a general medical condition, and separation anxiety disorder (American Psychiatric Association, 2000). Some apathy measures were designed for use among persons with dementia, specifically, while others were originally designed to operationalize apathy in other populations. The NPI, which provided the main measure of apathy in this study, was designed to evaluate behavioral disturbances in persons with dementia (Cummings et al., 1994; Kaufer et al., 2000) and has been credited with excellent reliability and validity and is

widely used (Cummings et al., 1994; Kaufer et al., 2000; Lerner et al., 2007). Conversely, the IA, providing the secondary measure of apathy in this study, was designed to provide an assessment of emotional, behavioral, and cognitive aspects of apathy in a broader population of patients with brain disorders such as AD, Parkinson's disease, and mild cognitive impairment (Robert et al., 2002).

Presence of apathy as measured by both the NPI-Apathy and IA demonstrated a highly significant relationship (Fisher's exact, p=.002), supporting the construct validity of the IA in comparison to the NPI-Apathy. However, there was not complete congruence between measures in detecting apathy. Three additional participants were identified as having apathy based on operationalization of apathy by the IA as compared to the NPI-Apathy. It may be that the emotional, behavioral, and cognitive dimensions of apathy measured by the IA provide a more inclusive measure of apathy. It may also be that the differential endorsements of apathy, as measured by the IA, for the three participants are false-positives. Further research is needed to validate and explain this observation.

The IA demonstrated excellent internal consistency in this study (Cronbach's alpha= .886, n=3), across the IA subscales among the subsample of participants for whom IA data were available. This result is comparable the overall reliability of the IA Caregiver (Cronbach's alpha=0.84) as reported in the literature (Robert et al., 2002). Original authors of the IA (Robert et al., 2002) established concurrent validity for the IA Caregiver by comparing the IA individual item (subscale) and total scores with the NPI-Apathy (Robert et al., 2002). Based on original analyses by IA researchers, Lack of Initiative and Lack of Interest subscales, pertaining to the behavioral and cognitive domains of apathy, were significantly correlated with the NPI-Apathy

(r=.22-.66; p<.05-p<0.001). In this study, IA subscale and IA total scores were highly significantly correlated with both presence and severity of apathy as measured by the NPI tool.

Predictors of the Presence of Apathy

The identification of background factor and proximal factor variables associated with the presence and severity of apathy were an important aim of this study.

Individual Associations. The relationship between gender and presence of apathy (NPI-Apathy) was not significant in this study (X^2 (1, N = 57) =3.697, p=.055), though men were more likely than women to exhibit apathy. Results were consistent with limited literature describing a higher prevalence of apathy among men with AD than among women with AD. In a cohort study of 491 persons with AD, participants exhibiting apathy were mostly men (X^2=8.74, p=0.003) (Vilalata-Franch et al., 2013). There was not a significant relationship between cognition (SIB total score) and presence of apathy as measured by the NPI-Apathy in this study (t(55) =1.652, p=.104). However, the relationship between cognition (SIB total score) and presence of apathy as measured by the IA *(*t(16) =3.397, p=.004) was significant.

In accordance with the literature, it was hypothesized that persons dwelling in dementia-specific care facilities may display less apathetic NDB than persons living in non-dementia-specific care settings. The hypothesis was based on the fact that dementia special care units within long-term care facilities often provide a modified social environment in the form of specialized programming, specialized staff, and family involvement (Maas, 1988). Mass and Buckwalter (1990) identified a significant decrease in behavioral symptoms in the special care unit experimental group of an intervention study. The hypothesized lower presence and severity of apathy among persons in dementia special care units was not supported by the current study results. These findings may mean that a larger sample size is required to test this hypothesis, or

that the residence and AS measures did not adequately capture relevant components of social environment (proximal factor) in the context of apathy.

Modeling the Presence of Apathy. NPI-Apathy data were used as the main Aim 1 outcome variable, as these data were more comprehensive than the IA data available for a subset of the sample (n=22). However, hierarchical logistic regression, with background factor variables [main demographic variables (age, gender) and cognition (SIB total score)] as block one variables, proximal factor variables [social environment as measured at time of data collection] as the block 2 variables, and function (FAST total score) and number of *APOE4* alleles as block three variables did not successfully predict the presence of apathy.

Predictors of the Severity of Apathy

Individual Associations. Study participants who scored lower on the SIB, indicating more compromised cognitive function, were more likely to demonstrate more severe apathy as measured by the NPI-Apathy, IA total score and all three IA domains of apathy. This may be because, according to Volicer and colleagues (1999), cognitive dysfunction greatly limits one's ability to engage in independent activities that he or she might have enjoyed before the onset of dementia or AD. It is interesting to note that the most significant IA subscale correlation was between cognition (SIB total score) and Lack of Interest. This lack of interest in activities previously enjoyed is, indeed, a contributor to apathy in persons with AD. The findings related to apathy and cognition in this study also support work by Algase and colleagues (1996), NDB model theorists, who indicated that the number of NDBs significantly increases with greater cognitive impairment. Frequency and severity of apathy, conceptualized as a NDB, increased with greater cognitive impairment among study participants.

Modeling the Severity of Apathy. Based on Aim 1 analyses, a combination of background factor variables [main demographic variables (age, gender) and cognition (SIB total score)], function (FAST total score), and number of *APOE4* alleles served as the most significant predictors of apathy, predicting 24.5% of the variance in apathy severity (NPI-Apathy) (F=2.370, p=.046). However, individual background factor variables were not predictors of apathy severity on their own, controlling for function (FAST total score) and number of *APOE4* alleles.

Background factor and proximal factor predictors of apathy, the NDB outcome variable, were associated with apathy severity more than the presence of apathy in this study. Additionally, individual background factor variable were not predictors of apathy severity on their own, controlling for function (FAST total score) and number of *APOE4* alleles. On one hand, these observations may reflect more statistical power to predict apathy when considering apathy as a continuous level factor (severity). On the other hand, these findings may reflect the possibility that background factor and proximal factor variables differentially influence the presence versus the severity of apathy among persons with AD. Background factor variables such as *OXTR* genotype status and cognitive abilities may affect the presence of apathy and the severity of apathy differently than variables related to social environment (proximal factor) in different ways among persons with AD.

***Oxytocin Receptor (OXTR)* gene as a Predictor of the Presence and Severity of Apathy.** The examination of a role for OT in the behavioral symptom of apathy was a key and novel aim of this study. OT has recently been discussed as a common regulatory element of the social environment and stress response (Smith & Wang, 2012). OT has also been associated with stress-induced risks on mental and physical health (Smith & Wang, 2012). While studies have begun to consider a possible role of pathological OT signaling in psychiatric disorders like

schizophrenia (Averbeck, 2010), autism spectrum disorders (Lerer et al., 2008) and Attention Deficit Hyperactivity Disorder (ADHD) (Park et al., 2010), the relationship between AD and *OXTR* has not been examined to date in published literature. OT may be a biomarker of social distress that accompanies gaps or problems with social relationships dependent on seeking close connections or association with others (Taylor, 2006).

Apathy in AD contains an emotional deficit component including low social engagement or blunted emotional response (Landes et al., 2001; Lerner et al., 2007; Marin, 1996), consistent with the study definition of apathy. Seeking close connections or association with others may be negatively affected by behavioral deficits like diminished initiation or poor persistence (Landes et al., 2001; Lerner et al., 2007) in activities or interactions, also common among persons exhibiting apathy and consistent with the study definition of apathy. Cognitive deficits such as lack of interest or lack of insight (Landes et al., 2001; Lerner et al., 2007; Marin, 1996; Robert et al., 2002) may further negatively contribute to social distress or problems with social relationships, like those being investigated in relationship to OT, a possible biomarker of social distress.

Relationships among *Oxytocin Receptor (OXTR)* gene SNPs and Presence of Apathy. It was hypothesized that variants within the *OXTR* gene were associated with apathy in persons with AD. No significant relationships emerged between genotype status for each of five *OXTR* SNPs and presence of apathy as measured by the IA and NPI-Apathy, nor in attempts to model *OXTR* SNPs as predictors of the presence of apathy (NPI-Apathy) in AD.

Relationships among *Oxytocin Receptor (OXTR)* gene SNPs and Severity of Apathy. Significant relationships were demonstrated between *OXTR* SNPs and apathy severity. A trend emerged between apathy severity (NPI-Apathy) and *OXTR2* (rs53576) (F= 2.747 (df=2), p=

.076), where persons with the AA genotype were more likely to display more severe apathy. Further, *OXTR2* genotype, in combination with cognition (SIB total score) and number of *APOE4* alleles, significantly predicted 19.4% of the variance in apathy severity (NPI-Apathy) (F=3.379, p=.027), with the AA genotype associated with more severe apathy. A trend emerged with the *OXTR3* (rs237885) variant, with *OXTR3* (rs237885) genotype, cognition (SIB total score), and number of *APOE4* alleles predicting 13.6% of the variance in apathy severity (NPI-Apathy) (F=2.414, p=.079), though the relationship did not reach significance.

In an association study of 350 participants with ADHD, Park and colleagues (2010) investigated whether *OXTR* polymorphisms previously implicated in autism were also associated with ADHD. An association with social cognitive impairments in a subset of 112 ADHD probands was found for a single *OXTR* SNP (rs53576) (F =5.24, p=0.007) (Park et al., 2010). Post-hoc analyses demonstrated that the AA genotype was associated with better social ability in comparison to the AG genotype among probands with ADHD. Interestingly, this is the same *OXTR* SNP (rs53576) that emerged as a significant predictor of apathy severity in persons with AD in this study. The genotype AA, associated with better social ability in persons with ADHD (Park et al., 2010), was also associated with more severe apathy among persons with AD in this study.

In a recent longitudinal study, *OXTR* was examined as a biological mechanism underlying prosocial behavior and stress-buffering among individuals enduring stressful life events and physical ailments (Poulin & Holman, 2013). Results indicated that prosocial behavior, namely charitable behavior, acted to successfully buffer stress among individuals with AA/AG genotypes of *OXTR* rs53576, but not among those with the GG genotype (Poulin &

Holman, 2013). In this study, participants with the AA genotype at *OXTR* rs53576 were more likely to demonstrate more severe apathy.

Further, Lucas-Thompson & Holman (2013) examined whether *OXTR* rs53576 buffered the combined impact of negative social environments, such as interpersonal conflict and constraint, and economic stress on post-traumatic stress (PTS) symptoms. Impaired daily functioning following collective stress related to the September 11th terrorist attacks was specifically examined in relationship to *OXTR* rs53576. Persons with GG genotype were compared to participants with any A allele. For those with an A allele, negative social environment significantly increased PTS symptoms, controlling for the level of economic stress experienced. However, in persons with the GG genotype, negative social environments predicted elevated PTS symptoms only in the context of high economic stress (Lucas-Thompon & Holman, 2013).

It is possible that persons with the AA genotype, associated with better social ability in persons with ADHD (Park et al., 2010) and prosocial behavior as a successful stress buffer during stressful life events and physical ailments (Poulin & Holman, 2013), also display more severe apathy in the context of AD. Individuals with this genotype may be more susceptible to the impact of negative social environments (Lucas-Thompon & Holman, 2013). Perhaps persons with the AA genotype (*OXTR* rs53576) also have a higher propensity for meaningful engagement. Or, these persons may be more likely to display apathy as a NDB in dementia if the need for meaningful engagement, which may be relatively higher, is not being met. While further research is necessary, study results provide insight into a newly examined relationship between AD and *OXTR*. The hypothesized involvement of variations in the *OXTR* gene and apathy in persons with AD was supported.

Relationships among Apathy and Functional Outcomes

The third primary goal of this study was to examine the relationship between apathy and functional status in the context of AD, with the hypothesis that more severe apathy is associated with decreased functional status in persons with AD, when controlling for severity of AD. Current study findings support this hypothesis.

Relationships between the Presence of Apathy and Function. Function (FAST score) significantly differed among persons exhibiting apathy and not exhibiting apathy as measured by both the NPI-Apathy and the IA. There was a significant association between the presence of apathy (NPI-Apathy) and function as measured by the FAC Cognitive status subscale, though there were not significant relationships between presence of apathy (NPI-Apathy) and the three remaining subscales. Presence of apathy as measured by the IA was significantly related to function as measured by the FAC Self Care and FAC Cognitive Status subscales. There were not significant relationships between presence of apathy (IA) and the two remaining subscales. Therefore, presence of apathy more consistently demonstrated an association with cognitive status aspects and self care aspects of function.

For this reason, it was important to examine the predictive ability of presence of apathy on functional status, while controlling for cognition. Multiple linear regression was used to examine the influence of presence of apathy (NPI-Apathy), controlling for cognition (SIB total score), on function (FAST score). Presence of apathy (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted 51.4% of the variance in function as measured by FAST score ($F=28.587$, $p<.0001$). Additionally, presence of apathy (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted 25.5% of the variance in function as measured by the FAC Self Care subscale ($F=9.523$, $p<.0001$) and 47.5% of the variance in function as

measured by the FAC Cognitive Status subscale (F=24.409, p<.0001). When controlling for cognition, presence of apathy remained a significant predictor of function as measured by the FAST scale and both the Self Care and Cognitive Status subscales of the FAC. Presence of apathy (NPI-Apathy), controlling for cognition (SIB total score), best predicted overall function as measured by the FAST scale.

Relationships between Severity of Apathy and Function. Apathy severity demonstrated a significant relationship with function as measured by FAST score. Significant relationships were also identified between apathy severity and function (FAST score) across all three apathy domains of the IA. Apathy severity (NPI-Apathy) was significantly correlated with function as measured by three FAC subscales: Self Care, Cognitive Status, Agitated Behaviors, but not with function as measured by the FAC Inappropriate behaviors subscale. Apathy severity (IA) was significantly correlated with function as measured by the FAC Cognitive Status subscale, but not with the three remaining subscales. Overall, apathy severity was consistently significantly correlated with function. Apathy severity was most often correlated with cognitive status dimensions of function. Apathy severity, as measured by the NPI-Apathy, demonstrated significant relationships with self-care, cognitive status, and selected behavioral aspects of function. Given these findings, the examination of the predictive ability of apathy severity on functional status was an important next step.

Severity of apathy as measured by the NPI-Apathy, controlling for cognition (SIB total score), significantly predicted 50.7% of the variance in function as measured by FAST score (F=27.774, p<.0001) Additionally, apathy severity (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted 26.6% of the variance in function as measured by the FAC Self Care subscale (F=2.513, p<.0001) and 48.8% of the variance in function as measured by the

FAC Cognitive Status subscale (F=25.766, p<.0001). Finally, apathy severity (NPI-Apathy), controlling for cognition (SIB total score), significantly predicted 10.9% of the variance in function as measured by the FAC Agitated Behaviors subscale (F=3.301, p=.044).

When controlling for cognition, severity of apathy remained a significant predictor of function as measured by the FAST scale and of function as measured by three of four FAC subscales. Specifically, apathy, controlling for cognition, significantly predicted self-care, cognitive, and select behavioral aspects of function. Apathy severity, controlling for cognition, also successfully predicted function as measured by the FAC Agitated Behaviors subscale, but not function as measured by the FAC Inappropriate Behaviors subscale. Severity of apathy (NPI-Apathy), controlling for cognition (SIB total score), best predicted function as measured by the FAST scale, accounting for over half of the variance in function. However, the model predicting apathy severity (NPI-Apathy), controlling for cognition, predicted a similar percentage (48.8%) of the variance in cognitive aspects of function (FAC Cognitive Status subscale).

Study findings support evidence that pronounced deficits in global cognition and instrumental abilities, as well as compromised nutritional status exist in persons with apathy and AD (Benoit et al., 2008; Lam et al., 2008; Norton et al., 2001). Moreover, study data are consistent with literature that demonstrates apathy is related to functional outcomes in AD, independent from cognitive status (Benoit et al., 2008). The study by Benoit and colleagues (2008), like the current study, utilized the NPI-Apathy but evaluated functional outcomes using the Inventory for Activities of Daily Living (IADL) (Lawton, 1969). Their models accounted for 44% of the variance in instrumental activities of daily living, based on apathy and executive cognitive dysfunction (Benoit et al., 2008). Current study results confirm the ability to predict

functional impairment in AD based on apathy, while controlling for cognition (Benoit et al., 2008), offering two models accounting for a large portion of the variance in apathy.

Current study results related to the relationship between apathy and function contradict work by Yu and colleagues (2006), which found that, despite a high prevalence of passivity, physical function was not related to passivity (Yu et al., 2006). These differences in results may be explained by differences in study measures, as measures may capture different aspects of apathy/passivity and function. For example, Yu and colleagues (2006) measured passivity using the Passivity in Dementia Scale (PDS) and physical function by direct observation using the physical capacity subscale of the Psychogeriatric Dependency Rating Scale (PGDRS). These differences may also suggest that passivity and apathy are distinct phenomena, necessitating further conceptual and empirical work.

Limitations

Potential limitations of this research are acknowledged. Participating facilities were identified by convenience to the parent study. Eligible residents within the facilities were recruited via convenience sampling, though all eligible participants had the opportunity to participate, resulting in data available for 66 participants. However, access to this vulnerable population is frequently restricted, resulting in this strategy as the most feasible method for descriptive research. The collection of some information from participants' legal representatives, as well as practice variability in AD diagnoses, is also acknowledged as a limitation.

A sample size of 66 is a limitation when looking at five *OXTR* SNPs, though online power calculations revealed that a sample of 66 participants yields 80% power to detect a moderate effect size (0.215) with an alpha level of 0.05 and 5 predictor variables (Soper, 2012). Being powered for a moderate effect size, however, is an added limitation. The genotype effect

of the five *Oxytocin Receptor* (*OXTR)* gene (rs2268491, rs6770632, rs237885, rs53576, rs237895) variants utilized in this study may, in fact, be small. In future studies, it may be advantageous to genotype additional SNPs across the *OXTR* gene with a larger sample size. The presence of missing data, though limited to 5% or less for most variables, is another limitation of this dissertation study.

The dissertation project did not address the physical environment of persons with AD and was limited in the ability to measure social environment. Social environment was measured using a categorical variable related to living situation available for all participants. However, to facilitate data analyses, these categories were further collapsed into two groups: dementia-specific environment and non dementia-specific environment. Data for social environment as measured by both residence at time of data collection and Ambiance Scale (AS) total score were available for a subset of the population (n=23). Correlations between social environment as measured by both residence at time of data collection and the AS and other study variables were largely lacking. It may be that the two variables used to measured social environment in this study did not adequately capture relevant proximal factor characteristics of social environment. The fact that participants came from various living environments (own home, long term care, assisted living), and therefore social environments, was also limiting. In future studies, a larger number of participants with AS scale data will be recruited. Alternative methods of measuring social environment as a proximal factor will also be explored.

Another potential limitation of this dissertation study, as in the parent study (Schutte et al., 2003; Schutte et al., 2011), is a restricted range in severity of AD among participants. To address this limitation, the investigators used measures that have been designed to be sensitive to change in severely cognitively and functionally impaired persons. Additionally, participants were

recruited from the community setting and all areas of the long-term care facilities located in the midwestern United States, increasing the likelihood of variation in stage and severity of AD. Nonetheless, there was substantial variability in phenotypes across the sample, despite recruitment primarily from institutional settings. While the overall cognitive characteristics of the sample suggested moderate impairment, as evidenced by a mean total SIB score of 50.66 (SD=39.09), the range of scores varied considerably.

The use of a newly developed apathy measure, the IA, among a portion of the sample is another limitation in this dissertation project. However, extensive literature review was conducted, and the IA was deemed valid, reliable, and appropriate for use in this population. The apathy subscale of the NPI-NH, credited with excellent reliability and validity (Cummings et al., 1994; Kaufer et al., 2000; Lerner et al., 2007), served as the primary measure of apathy with data available for the full sample. Study findings support the strong reliability of both the NPI and the IA, as well as the further benefit of assessing cognitive, behavioral and emotional domains of apathy using the IA.

Data collection was also cross-sectional and restricted to participants with little ethnic diversity residing in the midwestern United States, limiting generalizability of results. Aside from participant exclusion based on a diagnosis of Major Depressive Disorder, depression was not controlled for in this study. However, depression was not the main NDB outcome variables of interest. Medication use was also not considered, though antipsychotic use was identified as a risk factor for apathy in a cohort study of individuals with mild-moderate AD (Vialta-Franch, 2013).

Despite these limitations, this study provided a unique opportunity to contribute to the understanding of apathy in persons with AD. Few studies have attempted to model both

antecedents and consequences of apathy in a conceptually driven way. In addition, the integration of a genetic biomarker, such as OT, provides a helpful strategy for better understanding the biologic mechanism of apathy. Potential clinical markers or predictors of apathy were also expanded by the current research, with the possibility to influence future nursing practice.

Implications for Future Nursing Research

This dissertation study has several relevant implications for future nursing research. The study contained a large number of men, relative to the higher prevalence of AD among women (Alzheimer's Association, 2012; Plassman et al., 2007; Seshadri et al., 1997). Interestingly, while not significantly, men demonstrated a higher prevalence and severity of apathy than women in this study. Study findings also demonstrated a strong relationship between apathy and cognition, building on prior research. The IA instrument demonstrated reliability for examining cognitive, behavioral and emotional domains of apathy in persons with AD, also demonstrating concurrent validity with the highly accepted NPI-Apathy.

The theoretical framework utilized in the current study was an adaptation of the Need-Driven Dementia-Compromised Behavior Model (NDB) (Algase et al., 1996), with implications for theory. Additionally, the current study built upon the conceptualization of apathy as the expression of an unmet goal or need, consistent with the definition of a NDB by Algase and colleagues. The addition of function as a downstream sequela of apathy was also helpful in considering the consequences of apathy in persons with dementia. Apathy (NDB), controlling for cognition (background factor), successfully predicted function. Further examination of Severe Impairment Battery (SIB) subscales as related to apathy in persons with dementia may also add to this body of work. Additionally, future work would benefit from the inclusion of

improved measures of social environment (proximal factor), as the NDB conceptualizes that proximal factors could be manipulated to influence NDB.

Implications for Policy and Nursing Practice

Apathy presents particular caregiving challenges for family members, as persons with AD may be depressed, disengaged, or indifferent (Marin, 1996; Strauss & Sperry, 2002). Caregivers of persons with dementia exhibiting apathy report significant levels of distress and caregiver burden (Kaufer et al., 2000; Sanders et al., 2008). This caregiver burden may lead family members to more quickly institutionalize persons with AD, creating increased health care costs and utilization, contributing to the substantial costs of caring for persons with AD to American society (Alzheimer's Association, 2012). For the year 2012, it is estimated that the direct costs of caring for persons with AD to American society will total over $200 billion, including $140 billion in costs to Medicare and Medicaid (Alzheimer's Association, 2012).

Apathy often receives little attention unless families or healthcare providers recognize apathy and choose to pursue its treatment (Lerner et al., 2007). The lack of disruption of apathy symptoms as reported by caregivers in this study raises an interesting point about the potential barriers to identifying and treating apathy. If apathy is not viewed as disruptive, unlike agitation, wandering, and aggression as initially examined using the NDB model (Algase et al., 1996), apathy may not be viewed as a priority by healthcare providers. Apathy has not been prioritized as a NDB in the past. The current study demonstrated, however, that apathy negatively impacts function in persons with AD. Apathy, itself, may not be disruptive in a way that requires additional efforts by skilled health workers in long term care settings. However, given the deleterious impact of apathy on function in persons with AD, skilled workers in long term care settings, workers that are often in short supply, experience increased workloads. These functional

health issues and increased workloads for skilled health workers necessitate recognition and treatment of apathy by healthcare providers.

Current study results supported the hypothesized involvement of variations in *OXTR* in the underlying biologic pathway of apathy in persons with AD. It may be that persons with dementia and AA genotype (*OXTR* rs53576) have a higher propensity for meaningful engagement, or more profound apathetic responses to negative social environments. If that is the case, *OXTR* genotype may contribute to a risk profile for apathy among persons with dementia.

While apathy research remains in the early stages, emerging evidence supports apathy as a nurse sensitive outcome, and nonpharmacologic interventions show promise as symptom control modalities among persons with AD (Lerner et al., 2007; Politis et al., 2004; Wells & Dawson, 2000; W. Wood et al., 2009). If persons at greater risk for apathy have the potential to be identified, intervention studies designed to increase meaningful activity and social engagement in older adults with AD who are at higher risk for AD have the potential to decrease apathy and improve quality of life among this vulnerable population. These nonpharmacologic interventions must be sensitive to the underlying etiologic mechanism of apathy, providing a basis upon which to tailor interventions.

Conclusion

Despite the high prevalence and negative sequela associated with apathy, the literature provides little evidence of characteristics of persons with AD, including biologic factors that contribute to the presence and severity of apathy. The objective of the current study was to examine the extent to which, after adjusting for AD severity, resident characteristics and social environment factors predict the severity of apathy in persons with AD as a foundation for future intervention research. The study provided results beginning to contribute to a risk profile for

apathy among persons with dementia, addressing the identified knowledge gap and providing a foundation for the development of rigorous nonpharmacologic intervention studies in the future. Innovation is needed in order to help prevent and manage behavioral symptoms such as apathy, in persons with AD, an especially vulnerable population. To that end, there is a critical need for future research to further contribute to the understanding of the presence and severity of apathy in persons with dementia and to enhance the emerging risk profile for persons with dementia more likely to exhibit apathy.

APPENDICES

*MEASURES

**Note: All instruments purchased and/or used with permission as part of parent study (Schutte et al., 2003; Schutte et al., 2011)*

Genes, Environment & Behavior in Institutionalized Persons with AD

Resident Demographic Questionnaire

Item #	General Demographics (Circle Response)		
1	Resident Birthdate	_ _/ _ _/ _ _ _ _	
2	Date of institutionalization to current facility.	_ _/ _ _/ _ _ _ _	
3	Date of first institutionalization.	_ _/ _ _/ _ _ _ _	
4	Resident Gender	1	Male
		2	Female
5	Ethnic background	1	Non Hispanic White
		2	African American
		3	Asian/Pacific Islander
		4	Native American
		5	Hispanic
6	What is the last grade or year of school completed?	0	Don't know
		1	Attended Grade School
		2	Completed 8th Grade
		3	Attended High School
		4	Completed High School
		5	Attended College
		6	Associate Degree
		7	Bachelor's Degree
		8	Completed Some PostGraduate Courses
		9	Master's Degree
		10	Doctorate
7	What was resident's occupation?	0	Don't know
		1	Professional
		2	White Collar
		3	Blue Collar
		4	Farming/Agriculture
		5	Homemaker
		6	Other
		7	None

#	Symptom Onset & Evaluation				
8	What was the date of symptom onset?	_ _/ _ _ _ _			
9	What was the resident's age at symptom onset?	Year _ _ Month _ _			
10	What was the first symptom noticed?	Specify:			
11	Was a formal diagnosis of probable or possible AD made?	1	Yes		
		2	No		
		3	Don't Know		
12	Who made the diagnosis?	1	Family physician		
		2	Geriatrician		
		3	Neurologist		
		4	Psychologist		
		5	Other (specify:_____)		
	Were the following elements of a dementia evaluation completed?	1 = Yes	2 = No	3 = Don't Know	
13	Blood chemistries	1	2	3	
14	CT scan	1	2	3	
15	EEG	1	2	3	
16	MRI	1	2	3	
17	Lumbar puncture	1	2	3	

Item #	Comorbidities				
18	Has resident ever been diagnosed with any of the following conditions?	1= Yes	2 = No	3 = Don't Know	Age at Onset
19	Hypothyroidism	1	2	3	
20	CAD (heart attack)	1	2	3	
21	Hypertension	1	2	3	
22	NIDDM	1	2	3	

23	IDDM	1	2	3	
24	Parkinson Disease	1	2	3	
25	Depression	1	2	3	
26	Other psychiatric condition (anxiety, schizophrenia, manic-depressive).	1	2	3	
	Medication History				
27	Has resident ever taken any of the following prescribed medications on a daily basis for more than six months?	1= Yes	2 = No	3 = Don't Know	Name
28	Memory meds (e.g. Aricept, Exelon, Reminyl)	1	2	3	
29	Lipid lowering meds (Lopid, Lipitor, Mevacor)	1	2	3	
30	Blood pressure lowering meds (e.g. vasotec, atenolol, cardizem)	1	2	3	
31	Anti-inflammatory meds (e.g. ibuprofens)	1	2	3	
32	Alternative meds (e.g. Gingko supplement, Vit. E)	1	2	3	
33	Birth control containing hormones (pills, patch, implant, or injection)	1	2	3	
34	Estrogen or estrogen replacement therapy (e.g. Premarin, Estradiol, Ortho-Novum)	1	2	3	

	Environmental Exposures				
	Did resident ever:	1= Yes	2 = No	3 = Don't Know	Comments
35	Smoke regularly	1	2	3	
36	Consume alcohol to the extent that it interfered with daily functioning?	1	2	3	
37	Suffer a serious head injury that required medical care and/or caused unconsciousness?	1	2	3	

*SEVERE IMPAIRMENT BATTERY (SIB)

**Note: The Severe Impairment Battery (SIB) is a purchased instrument, and the scoring sheet could not be included due to formatting restrictions.*

Description: Assesses severe dementia in the elderly

Authors: Swihart, A. A, Boller, F., Saxton, J., & McGonigle, K. L.

Publication Year: 1993

Copyright: Pearson Education Limited

Instrument for Purchase: http://www.pearsonclinical.co.uk

Ambiance Scale

Instructions: Visually scan the target area and rapidly circle the number reflecting your immediate impressions. You may re-scan if you do not have an impression pertaining to a given item, but do not think much about your answers**. Record your immediate impressions.**

Ambiance Scale

Embellished	-2	-1	0	1	2	Stark
Stimulating	-2	-1	0	1	2	Custodial
Unpretentious	-2	-1	0	1	2	Pretentious
Colorful	-2	-1	0	1	2	Drab
Warm	-2	-1	0	1	2	Cold
Peaceful	-2	-1	0	1	2	Chaotic
Welcoming	-2	-1	0	1	2	Impersonal
Informal	-2	-1	0	1	2	Formal
Novel	-2	-1	0	1	2	Boring

*Neuropsychiatric Inventory (Nursing Home Version) Questions

***** *Note: Minimally reformatted from original version*

A. DELUSIONS (NA)

Does the resident have beliefs that you know are not true? For example, saying that people are trying to harm him/her or steal from him/her? Has he/she said that family members or staff are not who they say they are or that his/her spouse is having an affair? Has the resident had any other unusual beliefs?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐N/A

1. Does the resident believe that he/she is in danger – that others are planning to hurt him/her or have been hurting him/her?	☐ Yes	☐ No
2. Does the resident believe that others are stealing from him/her?	☐ Yes	☐ No
3. Does the resident believe that his/her spouse is having an affair?	☐ Yes	☐ No
4. Does the resident believe that his/her family, staff members, or others are not who they say they are?	☐ Yes	☐ No
5. Does the resident believe that television or magazine figures are actually present in the room? (Does he/she try to talk or interact with them?)	☐ Yes	☐ No
6. Does he/she believe any other unusual things that I haven't asked about?	☐ Yes	☐ No

Comments: _____
_____

If the screening question is confirmed, determine the frequency and severity of the delusions.

Frequency:

☐ 1. Rarely – less than once per week
☐ 2. Sometimes – about once per week
☐ 3. Often – several times per week but less than every day
☐ 4. Very often – one or more per day

Severity:

☐ 1. Mild – delusions present but seem harmless and does not upset the resident that much.
☐ 2. Moderate – delusions are stressful and upsetting to the resident and cause unusual or strange behavior.
☐ 3. Severe – delusions are very stressful and upsetting to the resident and cause a major amount of unusual or strange behavior

Occupational Disruptiveness: How much does this behavior upset you and/or create more work for you?

☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (some change in work routine, but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities

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B. HALLUCINATIONS (NA)

Does the resident have hallucinations – meaning, does he/she see, hear, or experience things that are not present? (If "Yes," ask for an example to determine if in fact it is a hallucination). Does the resident talk to people who are not there?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐N/A

1. Does the resident act as if he/she hears voices or describe hearing voices?	☐ Yes	☐ No
2. Does the resident talk to people who are not there?	☐ Yes	☐ No
3. Does the resident see things that are not present or act like he/she sees things that are not present (people, animals, lights, etc)?	☐ Yes	☐ No
4. Does the resident smell things that others cannot smell?	☐ Yes	☐ No
5. Does the resident describe feeling things on his/her skin or act like he/she is feeling things crawling or touching him/her?	☐ Yes	☐ No
6. Does the resident say or act like he/she tastes things that are not present?	☐ Yes	☐ No

7. Does the resident describe any other unusual sensory experiences?

Comments: _____
_____

If the screening question is confirmed, determine the frequency and severity of the hallucinations.

<u>Frequency:</u>

☐ 1. Rarely – less than once per week
☐ 2. Sometimes – about once per week
☐ 3. Often – several times per week but less than every day
☐ 4. Very often – one or more per day

Severity:

☐ 1. Mild – hallucinations are present but seem harmless and do not upset the resident that much.
☐ 2. Moderate – hallucinations are stressful and upsetting to the resident and cause unusual or strange behavior.
☐ 3. Severe – hallucinations are very stressful and upsetting to the resident and cause a major amount of unusual or strange behavior

Occupational Disruptiveness: How much does this behavior upset you and/or create more work for you?

☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (some change in work routine, but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities

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C. AGITATION/AGGRESSION (NA)

Does the resident have periods when he/she refuses to let people help him/her? Is he/she hard to handle? Is he/she noisy or uncooperative? Does the resident attempt to hurt or hit others?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐N/A

1. Does the resident get upset when people are trying to care for him/her or resist activities such as bathing or changing clothes?	☐ Yes	☐ No
2. Does the resident always want things his/her own way?	☐ Yes	☐ No
3. Is the resident uncooperative, resistive to help from others?	☐ Yes	☐ No
4. Does the resident have any other behaviors that make him/her hard to handle?	☐ Yes	☐ No
5. Does the resident shout, make loud noises, or swear angrily?	☐ Yes	☐ No
6. Does the resident slam doors, kick furniture, throw things?	☐ Yes	☐ No
7. Does the resident attempt to hurt or hit others?	☐ Yes	☐ No
8. Does the resident have any other aggressive or agitated behaviors?	☐ Yes	☐ No

Comments: _____
_____

If the screening question is confirmed, determine the frequency and severity of the agitation/aggression.

<u>Frequency:</u>

☐ 1. Rarely – less than once per week
☐ 2. Sometimes – about once per week
☐ 3. Often – several times per week but less than every day
☐ 4. Very often – one or more per day

Severity:

☐ 1. Mild – behavior is stressful for the resident, but can be controlled by the caregiver.
☐ 2. Moderate – behaviors are stressful for and upsetting to the resident and are difficult to control
☐ 3. Severe – agitation is very stressful or upsetting to the resident and is very difficult or impossible to control. There is a possibility they may injure themselves and medications are often required.

Occupational Disruptiveness: How much does this behavior upset you and/or create more work for you?

☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (some change in work routine, but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities

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D. DEPRESSION/DYSPHORIA (NA)

Does the resident seem sad or depressed? Does he/she say that he/she feels sad or depressed? Does the resident cry at times?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐N/A

1. Does the resident cry at times?	☐ Yes	☐ No
2. Does the resident say, or act like he/she is depressed?	☐ Yes	☐ No
3. Does the resident put him/herself down or say that he/she feels like a failure?	☐ Yes	☐ No
4. Does the resident say that he/she is a bad person or deserves to be punished?	☐ Yes	☐ No
5. Does the resident seem very discouraged or say that he/she has no future?	☐ Yes	☐ No
6. Does the resident say he/she is a burden to the family or that the family would be better off without him/her?	☐ Yes	☐ No
7. Does the resident talk about wanting to die or about killing him/herself?	☐ Yes	☐ No
8. Does the resident show any other signs of depression or sadness?	☐ Yes	☐ No

Comments: _____
_____

If the screening question is confirmed, determine the frequency and severity of the depression.

<u>Frequency:</u>

☐ 1. Rarely – less than once per week
☐ 2. Sometimes – about once per week
☐ 3. Often – several times per week but less than every day
☐ 4. Very often – one or more per day

Severity:

☐ 1. Mild – depression is stressful for the resident, but will usually change with the help of a caregiver.
☐ 2. Moderate – depression is stressful for the resident and is difficult to change by the caregiver.
☐ 3. Severe – depression is very upsetting and stressful for the resident and is very difficult or impossible to change.

Occupational Disruptiveness: How much does this behavior upset you and/or create more work for you?

☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (some change in work routine, but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities

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E. ANXIETY **(NA)**

Is the resident very nervous, worried, or frightened for no reason? Does he/she seem very tense or unable to relax? Is the resident afraid to be apart from you or from others that he/she trusts?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐N/A

1. Does the resident say that he/she is worried about planned events such as appointments or family visits?	☐ Yes	☐ No
2. Does the resident have periods of feeling shaky, unable to relax, or feeling very tense?	☐ Yes	☐ No
3. Does the resident have periods of (or complain of) shortness of breath, gasping, or sighing for no apparent reason other than being nervous?	☐ Yes	☐ No
4. Does the resident complain of butterflies in his/her stomach, or of racing or pounding of the heart because of being nervous? (Symptoms not explained by ill health)	☐ Yes	☐ No
5. Does the resident avoid certain places or situations that make him/her more nervous such as meeting with friends or participating in ward activities?	☐ Yes	☐ No
6. Does the resident become nervous and upset when separated from you or from others that he/she trusts? (Does he/she cling to you to keep from being separated?)	☐ Yes	☐ No
7. Does the resident show any other signs of anxiety?	☐ Yes	☐ No

Comments: _____
_____

If the screening question is confirmed, determine the frequency and severity of the anxiety

Frequency:

☐ 1. Rarely – less than once per week
☐ 2. Sometimes – about once per week
☐ 3. Often – several times per week but less than every day
☐ 4. Very often – one or more per day

Severity:

☐ 1. Mild – anxiety is stressful for the resident but will usually change with the help of a caregiver.
☐ 2. Moderate – anxiety is stressful for the resident and is difficult to change by the caregiver.
☐ 3. Severe – anxiety is very upsetting and stressful for the resident and is very difficult or impossible to change.

Occupational Disruptiveness: How much does this behavior upset you and/or create more work for you?

☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (some change in work routine, but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities

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F. ELATION/EUPHORIA (NA)

Does the resident seem too cheerful or too happy for no reason? I don't mean normal happiness, but, for example, laughing at things that others do not find funny?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐N/A

1. Does the resident appear to feel too good or to be too happy?	☐ Yes	☐ No
2. Does the resident find humor and laugh at things that others do not find funny?	☐ Yes	☐ No
3. Does the resident seem to have a childish sense of humor with a tendency to giggle or laugh inappropriately (such as when something unfortunate happens to others)?	☐ Yes	☐ No
4. Does the resident tell jokes or say things that are not funny to others but seem funny to him/her?	☐ Yes	☐ No
5. Does the resident show any other signs of feeling too good or being too happy?	☐ Yes	☐ No

Comments: _____
_____

If the screening question is confirmed, determine the frequency and severity of the elation/euphoria.

Frequency:

☐ 1. Rarely – less than once per week
☐ 2. Sometimes – about once per week
☐ 3. Often – several times per week but less than every day
☐ 4. Very often – one or more per day

Severity:

☐ 1. Mild – resident is too happy at times.
☐ 2. Moderate – resident is too happy at times and this sometimes causes strange behavior.
☐ 3. Severe – resident is almost always too happy and finds nearly everything to be funny.

Occupational Disruptiveness: How much does this behavior upset you and/or create more work for you?

☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (some change in work routine, but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities

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G. APATHY/INDIFFERENCE (NA)

Does the resident sit quietly without paying attention to things going on around him/her? Has he/she lost interest in doing things or lack motivation for participating in activities? Is it difficult to involve the resident in conversation or in group activities?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐N/A

1. Has the resident lost interest in the world around him/her?	☐ Yes	☐ No
2. Does the resident fail to start conversation? (score only if conversation is possible)	☐ Yes	☐ No
3. Does the resident fail to show emotional reactions that would be expected (happiness over the visit of a friend or family member, interest in the news or sports, etc.)?	☐ Yes	☐ No
4. Has the resident lost interest in friends and family members?	☐ Yes	☐ No
5. Is the resident less enthusiastic about his/her usual interests?	☐ Yes	☐ No
6. Does the resident sit quietly without paying attention to things going on around him/her?	☐ Yes	☐ No
7. Does the resident show any other signs that he/she doesn't care about doing new things?	☐ Yes	☐ No

Comments: _____
_____

If the screening question is confirmed, determine the frequency and severity of the apathy/indifference.

Frequency:

☐ 1. Rarely – less than once per week
☐ 2. Sometimes – about once per week
☐ 3. Often – several times per week but less than every day
☐ 4. Very often – one or more per day

Severity:

☐ 1. Mild – resident has a loss of interest in things at times, but this causes little change in their behavior or participation in activities.
☐ 2. Moderate – resident has a major loss of interest in things, which can only be changed by powerful events such as visits from close relatives or family members.
☐ 3. Severe – resident has completely lost interest and motivation.

Occupational Disruptiveness: How much does this behavior upset you and/or create more work for you?

☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (some change in work routine, but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities

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H. DISINHIBITION (NA)

Does the resident do or say things that are not usually one or said in public? Does he/she seem to act impulsively without thinking? Does the resident say things that are insensitive or hurt people's feelings?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐N/A

1. Does the resident act impulsively without thinking of the consequences?	☐ Yes	☐ No
2. Does the resident talk to total strangers as if he/she knew them?	☐ Yes	☐ No
3. Does the resident say things to people that are insensitive or hurt their feelings?	☐ Yes	☐ No
4. Does the resident say crude things or make inappropriate sexual remarks?	☐ Yes	☐ No
5. Does the resident talk openly about very personal or private matters not usually discussed in public?	☐ Yes	☐ No
6. Does the resident fondle, touch, or hug others in ways that are not appropriate?	☐ Yes	☐ No
7. Does the resident show any other signs of loss of control of his/her impulses?	☐ Yes	☐ No

Comments: _____
_____

If the screening question is confirmed, determine the frequency and severity of the disinhibition.

<u>Frequency:</u>

☐ 1. Rarely – less than once per week
☐ 2. Sometimes – about once per week
☐ 3. Often – several times per week but less than every day
☐ 4. Very often – one or more per day

Severity:

☐ 1. Mild – resident acts impulsively at times, but behavior is not difficult to change by caregiver.
☐ 2. Moderate – resident is very impulsive and this behavior is difficult to change by the caregiver.
☐ 3. Severe – resident is almost always impulsive and this behavior is nearly impossible to change.

Occupational Disruptiveness: How much does this behavior upset you and/or create more work for you?

☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (some change in work routine, but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities

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I. IRRITABILITY/LABILITY (NA)

Does the resident get easily irritated or disturbed? Are his/her moods very changeable? Is he/she extremely impatient?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐N/A

1. Does the resident have a bad tempter, flying "off the handle" easily over little things?	☐ Yes	☐ No
2. Does the resident rapidly change moods from one to another, being fine one minute and angry the next?	☐ Yes	☐ No
3. Does the resident have sudden flashes of anger?	☐ Yes	☐ No
4. Is the resident impatient, having trouble coping with delays or waiting for planned activities or other things?	☐ Yes	☐ No
5. Is the resident easily irritated?	☐ Yes	☐ No
6. Does the resident argue or is he/she difficult to get along with?	☐ Yes	☐ No
7. Does the resident show any other signs of irritability?	☐ Yes	☐ No

Comments: _____
_____

If the screening question is confirmed, determine the frequency and severity of the irritability/lability.

Frequency:

☐ 1. Rarely – less than once per week
☐ 2. Sometimes – about once per week
☐ 3. Often – several times per week but less than every day
☐ 4. Very often – one or more per day

Severity:

☐ 1. Mild – resident is irritable at times, but behavior is not difficult to change by the caregiver.
☐ 2. Moderate – resident is very irritable and this behavior is difficult for the caregiver to change.
☐ 3. Severe – resident is almost always irritable and this behavior is nearly impossible to change.

Occupational Disruptiveness: How much does this behavior upset you and/or create more work for you?

☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (some change in work routine, but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities

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J. ABBERANT MOTOR BEHAVIOR (NA)

Does the resident have repetitive activities or "habits" that he/she performs over and over such as pacing, wheeling back and forth, picking at things, or winding string? (Do not include simple tremors or tongue movements).

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐N/A

1. Does the resident pace or wheel around the facility with no reason?	☐ Yes	☐ No
2. Does the resident open or unpack drawers or closets over and over?	☐ Yes	☐ No
3. Does the resident repeatedly put on and take off clothing?	☐ Yes	☐ No
4. Does the resident engage in repetitive activities such as handling buttons, picking, wrapping string, moving bed sheets, etc.?	☐ Yes	☐ No
5. Does the resident have repetitive activities or "habits" that he/she performs over and over?	☐ Yes	☐ No
6. Is the resident excessively fidgety?	☐ Yes	☐ No

Comments: _____
_____

If the screening question is confirmed, determine the frequency and severity of the aberrant motor activity:

Frequency:

☐ 1. Rarely – less than once per week
☐ 2. Sometimes – about once per week
☐ 3. Often – several times per week but less than every day
☐ 4. Very often – one or more per day

Severity:

☐ 1. Mild – resident has repetitive behaviors at times, but this does not change daily activities.
☐ 2. Moderate – repetitive behaviors of the resident are very noticeable but can be controlled with help from the caregiver
☐ 3. Severe – repetitive behaviors are very noticeable and upsetting to the resident and are difficult or impossible to control by the caregiver.

Occupational Disruptiveness: How much does this behavior upset you and/or create more work for you?

☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (some change in work routine, but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities

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K. SLEEP AND NIGHTTIME BEHAVIOR DISORDERS (NA)

This group of questions should be directed only to caregivers who work the night shift and observe the resident directly or have acceptable knowledge (e.g., receive regular morning report) of the resident's nighttime activities. If the caregiver is not knowledgeable about the patient's nighttime behavior, mark this category "NA".

Does the resident have difficulty sleeping (do not count as present if the resident simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? Is he/she awake at night? Does he/she wander at night, get dressed, or go into others' rooms?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐N/A

1. Does the resident have difficulty falling asleep?	☐ Yes	☐ No
2. Does the resident get up during the night (do not count if the resident gets up once or twice per night only to go to the bathroom and falls back asleep immediately)?	☐ Yes	☐ No
3. Does the resident wander, pace, or get involved in inappropriate activities at night?	☐ Yes	☐ No
4. Does the resident wake up at night, dress, and plan to go out, thinking that it is morning and time to start the day?	☐ Yes	☐ No
5. Does the resident wake up too early in the morning (before other residents)?	☐ Yes	☐ No
6. Does the resident have any other nighttime behaviors that we haven't talked about?	☐ Yes	☐ No

Comments: _____
_____

If the screening question is confirmed, determine the frequency and severity of the nighttime behavior.

Frequency:

☐ 1. Rarely – less than once per week
☐ 2. Sometimes – about once per week
☐ 3. Often – several times per week but less than every day
☐ 4. Very often – one or more per day

Severity:

☐ 1. Mild – nighttime behaviors are present but not too stressful for the resident.
☐ 2. Moderate – nighttime behaviors are present and disturb others in the nursing home; more than one type of nighttime behavior may be present.
☐ 3. Severe – nighttime behaviors are present and the resident is very disturbed during the night.

Occupational Disruptiveness: How much does this behavior upset you and/or create more work for you?

☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (some change in work routine, but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities

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L. APPETITE AND EATING CHANGES (NA)

Does the resident have an extremely good or poor appetite, changes in weight, or unusual eating habits (count as "N/A" if the resident is incapacitated and has to be fed)? Has there been any change in type of food he/she prefers?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐N/A

1. Does he/she have a poor appetite?	☐ Yes	☐ No
2. Does he/she have an unusually good appetite?	☐ Yes	☐ No
3. Has he/she lost weight?	☐ Yes	☐ No
4. Has he/she gained weight?	☐ Yes	☐ No
5. Does he/she have unusual eating behaviors such as putting too much food in his/her mouth at once?	☐ Yes	☐ No
6. Has he/she had a change in the kind of food he/she likes such as wanting too many sweets or other specific types of food?	☐ Yes	☐ No
7. Has he/she developed eating behaviors such as eating exactly the same types of food each day or eating the food in exactly the same order?	☐ Yes	☐ No
8. Have there been any other changes in appetite or eating that I haven't asked about?	☐ Yes	☐ No

Comments: _____
_____

If the screening question is confirmed, determine the frequency and severity of the changes in eating habits or appetite.

<u>Frequency:</u>

☐ 1. Rarely – less than once per week
☐ 2. Sometimes – about once per week
☐ 3. Often – several times per week but less than every day
☐ 4. Very often – one or more per day

Severity:

☐ 1. Mild – changes in appetite or eating are present but have not led to changes in weight and are not disturbing.
☐ 2. Moderate – changes in appetite or eating are present and cause minor changes in weight.
☐ 3. Severe – obvious changes in appetite or eating are present and cause changes in weight, are abnormal, or upset the resident.

Occupational Disruptiveness: How much does this behavior upset you and/or create more work for you?

☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (some change in work routine, but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities

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*APATHY INVENTORY – *IA CAREGIVER*

Name: **date:**
Type of evaluation:
First Evaluation
Follow up evaluation: time since the previous evaluation

1 – Emotional blunting FxS= /12

Is he/she is as affectionate and express emotion as usual?

Yes = 0 **No** = *rate frequency and severity*

FREQUENCY

Occasionally: less than once a week	**1**
Often: about once a week	**2**
Frequently: several times a week but less than everyday	**3**
Very frequently: essentially continuously present	**4**

SEVERITY

Mild	**1**
Moderate	**2**
Marked	**3**

2 – Lack of initiative FxS= /12

Is he/she initiates a conversation and or make decisions?
In daily life, does he/she refer to you when he makes a decision or when he is asked a question?

Yes = 0 **No** = *rate frequency and severity*

FREQUENCY

Occasionally: less than once a week	**1**
Often: about once a week	**2**
Frequently: several times a week but less than everyday	**3**
Very frequently: essentially continuously present	**4**

SEVERITY

Mild	**1**
Moderate	**2**
Marked	**3**

**Note: Minimally reformatted from one-page original version*

3 – Lack of interest	**FxS=**	**/12**

Does he/she: Seem interested in the activities and plans of others?
Interested in friends and family members?
Enthusiastic about his/her usual leisure or professional interest?

Yes = 0 **No** = *rate frequency and severity*

FREQUENCY	
Occasionally: less than once a week	**1**
Often: about once a week	**2**
Frequently: several times a week but less than everyday	**3**
Very frequently: essentially continuously present	**4**
SEVERITY	
Mild	**1**
Moderate	**2**
Marked	**3**

TOTAL SCORE:	**(1+2+3)**	**/36**

IA – Inventaire Apathie – Centre Mémoire de Ressources et de Recherche – Nice - France

Gene, Environment & Behavior in Institutionalized Persons with AD
Functional Abilities Checklist (FAC)

	Functional Ability **(Consider functional ability over last 7 days.)**	**Frequency Rating** 1 = never 2 = seldom (less than 7 times per week 3 = frequently (daily) 4 = all of the time (multiple times per day)
1	Has difficulty in completing simple tasks on own, e.g., dressing, bathing	1 2 3 4
2	Requires supervision with eating	1 2 3 4
3	Uses utensils when eating	1 2 3 4
4	Eats food with fingers	1 2 3 4
5	Eats without assistance (if answer is "all the time" skip #6)	1 2 3 4
6	Won't allow assistance with eating	1 2 3 4
7	Requires assistance maintaining appearance	1 2 3 4
8	Requires assistance with toileting for bowel function	1 2 3 4
9	Requires assistance with toileting for bladder function	1 2 3 4
10	Urinates in places other than stool commode or bedpan/urinal (if wears adult briefs or has a catheter circle 5)	1 2 3 4 5
11	Has difficulty sleeping at night	1 2 3 4
12	Level of agitation increases at night	1 2 3 4
13	Needs to be watched so does not injure self, e.g., by careless smoking, leaving the stove on, falling	1 2 3 4
14	Destructive of materials around him, e.g., breaks furniture, throws food trays, tears up magazines	1 2 3 4
15	Accuses others of doing him bodily harm or stealing his possessions—when you are sure the accusations are not true	1 2 3 4
16	Threatens to harm others	1 2 3 4
17	Injures others	1 2 3 4
18	Invades privacy of others' possessions	1 2 3 4
19	Invades privacy of others' personal space	1 2 3 4
20	Removes clothing at inappropriate times	1 2 3 4
21	Has sudden changes of mood, e.g., gets upset angered, or cries easily	1 2 3 4
22	Loses things	1 2 3 4
23	Becomes confused and does not know where he/she is	1 2 3 4

24	Has trouble remembering recent events	1	2	3	4
25	Has trouble remembering non-recent events	1	2	3	4
26	Spends time either sitting or in apparently purposeless activity	1	2	3	4
27	Wanders at night	1	2	3	4
28	If left alone wanders aimlessly during the day	1	2	3	4

Functional Assessment Staging (FAST)

FAST Stage	Functional Assessment (Consider functional ability over last 7 days.)	Score (circle)
1	No difficulties, either subjectively or objectively.	1
2	Complains of forgetting location of objects; subjective word finding difficulties only.	2
3	Decreased job functioning evident to coworkers; difficulty in traveling to new locations.	3
4	Decreased ability to perform complex tasks (e.g. planning dinner for guests; handling finances; marketing).	4
5	Requires assistance in choosing proper clothing for the season or occasion.	5
6a	Difficulty putting clothing on properly without assistance.	6a
6b	Unable to bathe properly; may develop fear of bathing. Will usually require assistance adjusting bath water temperature.	6b
6c	Inability to handle mechanics of toileting (i.e. forgets to flush; doesn't wipe properly).	6c
6d	Urinary incontinence, occasional or more frequent.	6d
6e	Fecal incontinence, occasional or more frequent.	6e
7a	Ability to speak limited to about half a dozen words in an average day.	7a
7b	Intelligible vocabulary limited to a single word in an average day.	7b
7c	Non-ambulatory (unable to walk without assistance).	7c
7d	Unable to sit up independently.	7d
7e	Unable to smile.	7e
7f	Unable to hold head up.	7f

NOTE: Functional staging score = Highest FAST Stage checked

PROTECTION OF HUMAN SUBJECTS

PROTECTION OF HUMAN SUBJECTS

Human Subjects Involvement and Characteristics. Participants in this study were men and women with a diagnosis of possible or probable AD.

Inclusion criteria: 1) persons over the age of 21 years, 2) English-speaking, and 3) with a diagnosis of possible or probable AD based on criteria by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria (McKhann et al., 1984). This information was ascertained from participants' legal representatives or upon chart review.

Exclusion criteria: Participants with a comorbid diagnosis of a major psychiatric disorder, including major depression, schizophrenia, or bipolar disease, were excluded from this dissertation study.

Sources of Material. Following consent, members of the research team reviewed the medical record in order to collect health history, medical diagnoses, and dementia evaluation data. The investigator contacted the legal representative by phone in order to confirm these findings and to seek any additional information on family health history and diagnostic evaluation for AD. In only a few cases of discrepancy, the medical record data took priority over that provided by the participant's legal representative. In many cases, legal representatives requested that the investigator refer to participants' charts for confirmation of any information provided. The research team in each facility completed data collection for the participants with AD. Data collection also included obtaining a whole blood sample by phlebotomy or saliva sample by cheek swab as a DNA source. These samples were secured within the locked D. Schutte Laboratory and number-coded to protect participant identity. Data was collected for research purposes only. Questionnaires and samples were also number-coded to protect the identity of the participants. A master list of names and coded identifiers was created and stored in the PI's locked office in a locked file. Only the primary investigator and the major professor had access to the file during the dissertation project.

Potential Risks. Potential risks for participants involved in this study were minimal. This study was a cross-sectional study of persons with AD. Potential risks included:

1) Physical: a) Peripheral phlebotomy for a whole blood sample has a minimal risk of bruising and infection at the phlebotomy site. The procedure of collecting saliva samples causes little to no discomfort and has a minimal possibility of infection. Participants may feel awkward "spewing" into a specimen collection container. Every measure will be taken to protect the participant's privacy and dignity.
2) Psychological: a) Participation in this study may increase awareness of AD and potential long-term ramifications of the disease. As a result, psychological stress may occur on the part of participants or family caregivers. Education and basic counseling about AD are available from the primary investigator if appropriate. Referral services are additionally available for those with more extensive counseling and support needs.
   b) Participants may be concerned about participating in genetic research in relationship to insurability or in terms of concerns regarding the heritability of AD. No genotype information will be shared with the participant, the health care provider, the insurance company, or entered into the medical record. The participants will be informed that the

genetic analyses conducted in this study are not predictive or diagnostic. This information is provided during the consent process, both verbally and in writing.

Adequacy of Protection Against Risks

Recruitment and Informed Consent. Participants were recruited from both the community and long-term care facilities located in the midwestern region of the United States as part of the parent study, utilizing a consent procedure including evaluation of participant capacity to consent. Facility staff at the long-term care facilities identified potential participants with possible or probable AD. Facility staff then sought permission for the investigators to contact the legal representative. The research team contacted persons who agreed to receive further study information and provided additional information, clarified questions, and extended the invitation to participate. In most cases, potential participants demonstrated a lack of capacity to consent in which case informed consent was obtained from the legal representative for the individual with AD. Assent forms for the person with AD were also utilized if the investigator determined that the participant demonstrated study understanding and had the ability to provide a written signature. Once consent and assent were obtained, residents were screened to determine eligibility for the study. The investigator collected data about health history and medical diagnoses from the medical record, with verification from the legal representative, to determine the extent to which a comprehensive dementia diagnostic evaluation was completed and the established AD diagnostic criteria were met. As part of the parent study, these triangulated data were reviewed by Dr. D. Schutte to help to assure diagnostic accuracy. In the event that the triangulated data were incomplete or equivocal, the subject was not enrolled for data collection.

Protection Against Risk. Several strategies to protect human subjects were undertaken during this dissertation study. Whole blood samples were obtained by a trained phlebotomist, via a contracted service within each facility. Saliva sample collection was carried out by trained research team members. Additionally, care providers were made aware of whole blood sample collections and the need to monitor for potential bruising or infection. In the event of psychological or emotional distress related to an increased awareness of AD heritability, all subjects and their family members had access to genetic counseling, including emotional and psychological counseling, where appropriate, by the primary investigator and her major professor. However, this was not necessitated during the dissertation study. Several safeguards to ensure privacy of data were also undertaken. Coded ID numbers were used on the blood tube or saliva swab collection containers, DNA sample vials, genotype reports, and resident assessment instruments. The code key linking names and ID numbers was kept separately from other data. All paper records were maintained in locked files in a locked research office. In addition, published reports of results will not include subject identifiers. Because the clinical usefulness of the candidate AD genotype data remains experimental, results of the genotyping were not disclosed to subjects. Subjects were advised that they could withdraw their genotype data from the study analysis at any time without penalty. Similarly, it was made clear that DNA samples would be destroyed upon the request of the legal representative, though these requests were not made during the dissertation study. Following completion of this study, DNA samples continue to be stored with the coded ID numbers, and subjects have been informed that samples may be used to answer similar research questions with additional candidate AD genes. However, prior to

using the DNA samples for any non-AD related research, subjects will be re-contacted to obtain additional informed consent.

Potential Benefits of the Proposed Research to Human Subjects and Others

There is no direct benefit of this research to the participants; however, there is potential benefit for society at large. Results from this study will provide a better understanding of apathy and functional status in persons with AD, as well as *OXTR* as a candidate gene for apathy in persons with AD. Better understanding of apathy and its impact on functional status may lead to early intervention among persons at increased risk for apathy in AD, which may eventually result in a decrease in disease burden for society.

Importance of the Knowledge to Be Gained

Despite the growing prevalence of AD, in addition to the high prevalence and negative sequela associated with apathy, little is known about characteristics of residents with AD, and the environmental and biologic factors that contribute to the presence and/or severity of apathy in persons with AD. Oxytocin (OT) has been implicated as an important hormone in mother-infant bonding (Douglas, 2010) and was recently implicated as a moderator of human social behaviors with possible significance to social decision-making (Averbeck, 2010; Campbell, 2010). Thus, variations in the *Oxytocin Receptor (OXTR)* gene are hypothesized to be candidate modifiers of apathy in persons with AD.

The current knowledge gap prevents healthcare providers from properly identifying persons with apathy, identifying which individuals might be more prone to apathy, and identifying how resident characteristics and social environmental factors impact the presence and/or severity of apathy in persons with AD as well as subsequent functional outcomes. Further, the current knowledge gap limits the development of rigorous intervention studies to combat this problem.

The investigator's long-term research goal is to conduct intervention studies designed to increase meaningful activity and social engagement in this vulnerable population of older adults with AD as a means to decrease apathy and improve their quality of life. The objective of the current proposal and dissertation study is to examine the extent to which, after adjusting for AD severity, resident characteristics and social environment factors predict the severity of apathy in persons with AD as a foundation for intervention research. *OXTR* will be examined as an important potential modifier in the prediction of apathy in persons with AD. Particularly in persons in more advanced stages of AD, exploring a candidate marker for apathy is extremely innovative.

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