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**A MODEL OF AGITATED BEHAVIORAL SYMPTOMS IN PERSONS WITH
ALZHEIMER DISEASE**

by

KATHERINE KERO

DISSERTATION

Submitted to the Graduate School

of Wayne State University,

Detroit, Michigan

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

2020

MAJOR: NURSING

Approved By:

Advisor

Date

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DEDICATION

This dissertation is dedicated to everyone who suffers from age-related degenerative diseases, and to those who care for and about these individuals. Your battle is unique, but you are not alone. This work was completed with the remembrance of my grandmother Pearl who suffered from Parkinson's disease, and with thoughts of my grandmother Betty who suffers from dementia. They are both amazing women who continue to give me inspiration and courage.

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CHAPTER 1: INTRODUCTION

Background and Significance

Shifting Demographics

Over the past 100 years, advances in healthcare and reductions in family sizes have resulted in an aging population. Worldwide, aging trends are expected to accelerate in coming decades. The worldwide population of older adults is projected to double by 2050, while overall population growth will increase by only 34% during this period (He, Goodkind, & Kowal, 2016). Economically developed countries in Europe and the United States have already begun to gradually experience this demographic shift; countries in Latin America and Asia will face rapid demographic shifts in the next 30 years (He et al., 2016).

In the United States, the large generation of people born between the 1940's and mid 1960's known as the "Baby Boomers" are becoming older. Individuals in the Baby Boomer generation are expected to live longer than their ancestors. These two factors will result in the number of Americans aged 65 and older doubling over the next 20 years to about 72 million people (Alzheimer's Association & Centers for Disease Control and Prevention [AA & CDC], 2013). In addition to the increase in the absolute number of older adults, Senior Citizens are also beginning to represent a larger proportion of the United States population. Although they represented only 9% of the population in 1960, older adults will account for 20% of the United States population by 2030 (AA & CDC, 2013; Mather, Jacobsen, & Pollard, 2015). As older adults have greater health care needs, these demographic shifts present a challenge for the health care system.

While these "golden years" of life hold the opportunity for increased leisure and the enjoyment of the fruits of a life well lived, advanced age corresponds with an increased risk of

developing Alzheimer Disease (AD; Katz et al., 2012). AD is very common in older adults. One in ten people over the age of 65 has AD, and the risk increases with advancing age (AA, 2017). As a result of the aging population, the number of Americans with AD is expected to triple to 14 million people by 2050 (Mather et al., 2015).

Alzheimer Disease

AD is a chronic, progressive, and irreversible neurological disease. AD has an insidious onset; it results in the gradual loss of cognitive and functional abilities. At first, it may be difficult to distinguish typical age-related changes—such as occasional memory lapses, episodes of confusion, visual changes, or moodiness—from signs of AD (AA, 2017). In AD, problems with memory loss, problem solving, confusion, interpretation of spatial-visual information, communication, judgement, or mood disrupt daily life (AA, 2017). These problems worsen over time, and result in an inability to care for oneself, immobility, and death.

Despite the investment of billions of public and private research dollars over the past several decades, no cure for AD has been identified. The clearest risk factors for AD are non-modifiable genetic mutations, but even genetically-susceptible individuals have great heterogeneity in neuropathology and cognitive performance in older age (Wirth, Villeneuve, La Joie, Marks, & Jagust, 2014). Drugs have been investigated which may someday be used for prevention of AD by individuals who have genetic risks for developing AD-related neural pathologies, but more testing is needed to determine the safety and efficacy of these therapies (Rafii & Aisen, 2015).

Evidence for the prevention of AD is largely inconclusive, although some risk factors have been identified which may have an additive effect on the development of AD. Modifiable risk factors for AD may include cardiovascular disease, cerebrovascular lesions, diabetes

mellitus, hypertension, obesity, high cholesterol, smoking, alcoholism, high saturated fat diet, and depression (Solomon et al., 2014). Activities that have demonstrated a protective effect against AD include high levels of education, social engagement, mentally stimulating activities, a heart-healthy diet, physical exercise, adequate intake of vitamins A, B complex, C, D, and E, and medication such as anti-hypertensives, statins, hormone replacement therapy, and nonsteroidal anti-inflammatory drugs (Solomon et al., 2014). These risk and protective factors suggest an interaction between the pathophysiological processes of AD and other common chronic conditions.

In addition to its impact on individuals, AD also has an enormous impact on family members. As the disease advances, sufferers have an increased need for care and supervision (Okura et al., 2011). Over 15 million Americans are unpaid caregivers for individuals with AD, and their work is valued at over \$230 billion annually (AA, 2017). Informal caregivers are at a high risk for caregiver burnout, depression, anxiety, immune dysfunction, stroke, increased pain symptoms, and premature death (Fonareva & Oken, 2014; Hong, Han, Reistetter, & Simpson, 2016; Ivey, Allen, Liu, Parmelee & Zarit, 2017; Perkins et al., 2013; Sallim, Sayampanathan, Cuttilan, & Ho, 2015). These overburdened caregivers have more frequent doctor appointments, hospitalizations, and medication use resulting in an estimated \$10.9 billion in excess healthcare cost (Zhu et al., 2015).

Because of the long-term course of AD, these individuals may need care for many years. As AD symptoms worsen over time, the needs for care become more intense. Family caregivers may be supplemented by professional services such as adult day services or hired in-home caregivers. When the care needs or expenses become too great, individuals are moved into residential institutions such as assisted living facilities or nursing homes.

The cost of residential long-term care services is high. Assisted living costs over \$43,000 per year, and care provided in nursing homes costs \$82,000-\$92,000 per year (Genworth, 2016). As half of all older adults receiving Medicare benefits have less than \$64,000 in savings, these costs are unaffordable for most individuals (MetLife, 2012). When financial assets are depleted, Medicaid pays for long-term care (Centers for Medicare & Medicaid [CMS], 2017). The majority of long-term care residents, about 62%, are using the Medicaid program (Rudowitz & Garfield, 2018). The Medicare program is strained by these costs. Expenditures have increased 6.0% annually in 2006 to 2017 mostly due to the increasing enrollment of older adults with complex healthcare needs (Holahan & McMorrow, 2019). Given the enormous costs of long-term care, there is a clear financial incentive to help individuals remain in their homes for as long as possible.

The total costs of AD and dementia care paid in 2017 was estimated at \$259 billion (AA, 2017). AD is one of the most expensive medical conditions to the general public (Hurd, Martorell, Delavande, Mullen, & Langa, 2013). Sources of payments for AD related care include Medicare (51%), Medicaid (17%), out of pocket (22%; including personal savings, pensions, and Social Security), and other sources such as private insurance and unpaid care (11%; AA, 2017). Public sources of funding for care In addition to the high personal costs incurred as a result of AD, this disease represents a high cost burden on society as a whole.

Agitation

Beyond the physical and cognitive effects of AD, behavioral symptoms are also common. Behavioral or neuropsychiatric symptoms including agitation, anxiety, apathy, delusions, depression, disinhibition, elation, hallucinations, irritability, sleep disorders, or social withdrawal are common with AD (Cummings et al., 1994; McKhann et al., 2011). As with other

manifestations of AD, behavioral symptoms worsen with disease progression. In the early stages of AD, the prevalence of at least one behavioral symptom ranges from 12.8-66.0% (Köhler et al., 2016). Incidence of these symptoms increases over the course of the disease. Cumulative prevalence rates for at least one neuropsychiatric symptom range between 49 and 95% in individuals with advanced AD (Borsje, Wetzels, Lucassen, Pot, & Koopmans, 2015).

Of the many neuropsychiatric symptoms in AD, agitated behavioral symptoms are especially important. Agitation is a broad construct encompassing inappropriate verbalizations or physical movements that are unrelated to needs or represent an excessive response to needs (Cummings et al., 2015; Cohen-Mansfield & Billig, 1986). Agitation can include both aggressive and nonaggressive behaviors (Cohen-Mansfield & Billig, 1986). Examples of agitated behaviors include pacing or wandering, inappropriate dress or disrobing, screaming, repeated questions, and hitting (Cohen-Mansfield, 1991). Although sometimes discussed as distinct phenomena, aggression, fighting, irritability, resistance to care, restlessness, wandering are closely related concepts which can be considered expressions of agitation when they occur in person with dementia and cause excess disability (Cummings et al., 2015; Fauth & Gibbons, 2014; Hurley et al., 1999; Kong, 2005).

Agitation occurs in over 71% of individuals with AD. Individuals with AD often experience distress over these symptoms, and quality of life is diminished with increasing levels of agitation (Hongisto et al., 2015). Agitated behavioral symptoms increase the need for care and supervision of individuals with AD (Okura et al., 2011). Caregivers report that agitation is the most difficult symptom of AD to manage (Chiao, Wu, & Hsiao, 2015). Caregiver distress and burnout related to agitated behavioral symptoms results in early institutionalization of persons with AD, and may increase the risk of elder abuse (Cooper et al., 2010; Gaugler,

Krichbaum, & Wyman, 2009; Pérez-Rojo, Izal, Montorio, & Penhale, 2009; VandeWeerd et al., 2013).

Despite these dismal consequences of agitation, treating agitation is challenging. A variety of promising social and environmental interventions have demonstrated no significant improvement in agitated behavior. Staffing ratios, aromatherapy, and light therapy do not appear to improve agitated behavioral symptoms (Livingston et al., 2014; Livingston et al., 2017; Zuidema et al., 2009).

A few interventions have been identified which may reduce agitation in some situations. Environmental and behavioral interventions which have demonstrated moderate improvements to agitated behavioral symptoms include music therapy, staff communication training and sensory interventions (Deudon et al., 2009; Livingston et al., 2014). Physical exercise has many benefits for persons with dementia including reduced agitation, improved cognitive performance, and improved mood (Brett, Traynor, & Stapley, 2016). However, many older adults including persons with AD have impaired mobility and are unable to access these benefits, and interventions to train staff to encourage exercise and social interactions are not effective in reducing agitation (Ballard et al., 2015).

Pharmacological interventions are sometimes used to reduce agitated behavioral symptoms in persons with AD. Although antipsychotic medications are sometimes effective in temporarily reducing certain agitated behaviors, their use is not routinely recommended as these drugs carry a high risk of side effects for older adults. Adverse side effects may include blood clots, cerebrovascular events, drowsiness, tremors or movement difficulties, functional and cognitive decline, and death (Foebel et al., 2016; Schneider, Dagerman, & Insel).

While some interventions have demonstrated modest improvements in agitated behavioral symptoms, effects of these interventions in the clinical setting are highly variable. To improve the effectiveness of current interventions and identify further interventions to improve agitated behavioral symptoms in persons with AD, a complete understanding of the causes of agitation is needed. A causal model of agitation will help organize and understand antecedent factors to allow more specific and effective interventions to be identified and developed.

Statement of Problem

AD is debilitating, costly, and widespread. Difficulties related to AD are projected to worsen in the future due to shifting demographics and lack of treatments. Given that the current state of the science of AD care offers no cure for the disease, mitigation of symptoms provides the best opportunity for intervention to improve quality of life and functional status for individuals with AD. Because agitated behavioral symptoms are the most detrimental and costly symptoms associated with AD (through high prevalence, reduced quality of life for individuals, increased caregiver burnout, increased risk of elder abuse, and increased risk of costly institutionalization), the management of symptoms of agitation is the most urgent research priority. At the present time, the nonpharmacological and pharmacological interventions to address agitated behavioral symptoms have been shown to be ineffective or risky. Furthermore, since most previous research investigates the direct effects of individual factors on agitation, it is unclear how the constellation of symptoms and environmental factors experienced by those with AD may contribute to the worsening or improvement of agitation. A holistic framework for understanding the causes and consequences of agitation is needed. Therefore, this dissertation proposes to identify factors that worsen or improve agitation, and how the resulting level of agitation impacts functional status.

Relevance to Nursing Knowledge

The phenomenon of agitated behavioral symptoms in persons with AD lends itself to study by nursing as it fits squarely within the Fawcett's definition of concepts of interest to nursing's metaparadigm including health, human beings, the environment and nursing (Fawcett & DeSanto-Madeya, 2013). Health is the most important metaparadigm concept within the phenomenon of functional performance in older adults with cognitive decline. It is the departure from normal cognitive health that defines conditions like AD, and the performance of functional roles that demonstrates a state of overall health. While studying this phenomenon, the nursing perspective emphasizes the view that persons with AD are human beings first and sufferers of a condition second. The environment is important to the study of agitated behavioral symptoms as it can either trigger symptoms or help reduce symptoms. Finally, the concept of nursing is important to the study this phenomenon because nurses and other caregivers are in a position to prevent and manage agitated behavioral symptoms in persons with AD.

Epistemology refers to the nature of knowledge and how knowledge can be known (Rodgers, 2005). In nursing, epistemology denotes knowledge that is accepted by members of the nursing discipline, the types and patterns of knowledge within nursing, and the evaluation criteria used by the discipline to accept or reject new knowledge claims (Schultz, 1988). The nature of knowledge that can be described about the phenomenon of agitated behavioral symptoms in persons with AD will be different depending on the disciplinary perspective from which the phenomenon is studied. Since this phenomenon is so closely related to the concepts of interest to the nursing discipline, there is an opportunity for nursing knowledge to be gained from the study of this topic.

One type of nursing knowledge is empirical knowledge. Empirical knowledge is gained by making systematic observations through research (Schultz, 1988). The credibility of empirical knowledge in research is dependent on adherence to widely-accepted research methods and the minimization of bias (Schultz, 1988). New claims of empirical knowledge related to the study of agitated behavioral symptoms in persons with AD which arise from the proposed research will be evaluated for credibility and utility to nursing on the basis of rigor of research methods, minimization of bias, and assessment of how these new claims fit into the extant body of literature surrounding the topic. Each additional claim of empirical knowledge can contribute to conceptual nursing knowledge through reflection and synthesis of multiple claims to identify patterns.

Conceptual nursing knowledge is a type of knowledge that extends beyond that which is known through personal experience; conceptual knowledge describes the patterns shared through multiple patient experiences or situations and explores these patterns through theories or models (Schultz, 1988). Conceptual knowledge is evaluated based on the degree to which theories or models are useful in describing patterns of experience with coherence and logical arguments (Schultz, 1988). Research to better understand the phenomenon of agitated behavior in persons with AD will contribute to conceptual knowledge in nursing by clarifying the relationship between the empirical observations of agitated behavioral symptoms in persons with AD to antecedents and consequences of these symptoms. These patterns in behavior will be framed within a model based on the nursing Theory of Unpleasant Symptoms (TOUS). The degree to which the model accurately and completely describes the observed phenomenon will validate the legitimacy of the TOUS. If the model accurately reflects the phenomenon, it will be a useful tool which can be applied to different nursing practice situations to improve the care of patients.

Statement of Purpose

The purpose of this dissertation is to test a model of the predictors and outcomes of agitated behavioral symptoms among persons with AD. The model will be structured by the theoretical concepts and relationships predicted in the Theory of Unpleasant Symptoms (Lenz, Supp, Gift, Pugh, & Milligan, 1995; Lenz, Pugh, Milligan, Gift, & Suppe, 1997). This nursing theory focuses on the antecedents and consequences of symptoms within a comprehensive framework. Antecedent factors are divided into three categories: situational, psychological, and physical factors. Examples of situational factors include environmental influences like physical surroundings and interpersonal factors such as social engagement and the influence of caregivers. Psychological factors include anxiety and depression. Physical factors include sleep, pain, hearing loss, and disease states such as AD with its resulting decline in cognitive capacity. Symptom consequences are conceptualized as performance-based outcomes such as functional ability, performance of activities of daily living, and quality of life. The TOUS provides a clear framework for understanding symptoms and proposes theoretical relationships between variables. However the TOUS has not been used to describe agitated behavioral symptoms and has never been applied to a population of persons with AD.

Specific Aims and Hypotheses

Aim 1:

Describe the phenomenon of agitated behavioral symptoms in persons with AD within the Theory of Unpleasant Symptoms.

Hypothesis: The Theory of Unpleasant Symptoms (TOUS) will adequately describe the antecedents and consequences of agitated behavioral symptoms in persons with AD.

Aim 2:

Determine the effect of situational (physical and social environment), psychological (anxiety, and depression), and physiological factors (comorbidities, pain, nutritional status, hearing, cognitive impairment, and fatigue) on agitated behavioral symptoms in persons with AD.

Hypotheses:

- (1) Supportive and stimulating physical and social environments will have a negative direct effect on agitation.
- (2) Comorbid psychological states will have a positive direct effect on agitation.
- (3) Comorbid physical conditions, pain, inadequate nutritional status, hearing loss, cognitive impairment, and fatigue will have a direct positive effect on agitation.

Aim 3:

Determine the effect of situational, psychological, and physical antecedent factors and agitation on performance outcomes (functional status and quality of life) in persons with AD.

Hypotheses:

- (1) Supportive and stimulating physical and social environments will have an indirect positive effect on functional status and quality of life through reduced agitation.
- (2) Comorbid psychological states will have an indirect negative effect on functional status and quality of life through increased agitation.
- (3) Comorbid physical conditions, pain, nutritional status, hearing loss, cognitive impairment, and fatigue will have an indirect negative effect on functional status through increased agitation.
- (4) Agitation will have a negative direct effect on functional status and quality of life.

Summary

As the population ages, problems related to AD will become increasingly burdensome in the coming years. Agitated behavioral symptoms in persons with AD are of chief concern because they are challenging to manage, have detrimental effects on individuals, and lead to costly consequences. A complete understanding of the antecedent factors is needed to identify future interventions to improve functional outcomes and quality of life for persons with AD. While previous work has been done to study simple relationships between isolated antecedents or consequences of agitation, this proposed research will build upon previous work by identifying the relative and combined impact of each antecedent variable on agitation, and determine how some of these factors may work together to exert a synergistic negative effect on functional performance. This knowledge will be used to identify opportunities for high impact interventions for future investigations.

The empirical and conceptual nursing knowledge gained through the study of this phenomenon will contribute to nursing science. Donaldson (2003) explains that nursing science is the science of human health within defined thematic and person-based health domains. In contrast, Schoenhofer (1993) proposes that the most straightforward definition of nursing research is a research question which is framed within a nursing theory. By either definition, the study of agitated behavioral symptoms of older adults with AD framed within the nursing TOUS will generate a type of unique nursing knowledge which supports the discipline of nursing and informs nursing practice.

CHAPTER 2: LITERATURE REVIEW AND THEORETICAL FRAMEWORK

The following review will discuss the state of the science related to AD and agitated behaviors among persons with AD including risk factors and associated outcomes. A discussion of gaps in the literature and conceptual challenges will follow. Finally, the application of the Theory of Unpleasant Symptoms framework to guide research related to agitated behavioral symptoms in persons with AD will be explained.

Alzheimer Disease Overview

Healthy individuals may experience changes in thinking as they age. Although crystallized intelligence (knowledge) and personality remain stable throughout the lifespan, fluid intelligence, working memory, and response time generally decline in healthy adults as they age (Blazer, Yaffe, & Karlawish, 2015; Bender & Raz, 2012; Harris, Brett, Johnson & Deary, 2016; Yuan, Voelkle, & Raz, 2018). Occasionally, marked changes in thinking become pathological in older adults. Symptoms of neuropathological changes, including a general loss of cognitive ability and memory impairment, are known as dementia. Although dementia symptoms may arise because of several different etiologies, the most common cause of dementia symptoms is AD. The 2011 National Institute on Aging-Alzheimer Association criteria define possible or probable AD as a persistent decline in cognitive function over time that interferes with usual activities, and includes impairments in learning, judgment, visuospatial abilities, language, or changes in personality (McKhann et al., 2011). A summary of neuropathological features of AD and possible etiologies of AD are reviewed in the following.

Neuropathology of Alzheimer Disease

For over 100 years, AD has been recognized as a neurological disease primarily affecting older adults. Although many scientific advances have been made in the past century, many

details about the neuropathological processes that result in AD have remained elusive. Much of what is known about the neurological disease states which result in the clinical expression of AD symptoms was learned from the postmortem analysis of the brain tissue of affected individuals. The microscopic and macroscopic pathologies identified in these early studies have allowed scientists to validate the correlations between postmortem pathologies and AD with living individuals with AD using MRI.

On the microscopic level, brain tissue of individuals with AD shows amyloid plaques and neurofibrillary tangles which define AD. Amyloid plaques are accumulations of pieces of the amyloid precursor protein called amyloid- β ($A\beta$; Okura et al., 2011). $A\beta$ proteins are found in the cortices and cerebral blood vessels of individuals with AD (Serrano-Pozo et al., 2011). In early stages of AD, $A\beta$ plaques tend to accumulate in the neocortex (Thal, Rüb, Orantes & Braak, 2002). As AD progresses, $A\beta$ plaques spread to cover the deeper allocortical and subcortical regions (Jucker, Mathias, & Walker, 2011). While $A\beta$ is present even in the brains of healthy individuals, a type of $A\beta$ that is prone to causing plaque buildup is present in excessive quantities in persons with AD (Puzzo et al., 2011; Shen & Kelleher, 2007).

Neurofibrillary tangles (NFT) composed of abnormally phosphorylated and misfolded tau proteins are considered a hallmark of AD (Perl, 2010). The quantity and distribution of NFT increases as AD progresses, and corresponds with increased dementia symptoms (Bierer et al., 1995). Neurons and synapses are lost in parallel to the formation of NFT, but it is unclear how the two phenomena are related (Serrano-Pozo, Frosch, Masliah, & Hyman, 2011).

Neuropathological changes with NFT in AD follow a very predictable pattern over time. Eva and Heiko Braak (1991) categorized these changes into six stages commonly referred to as Braak stages. The beginning stages are defined by diffuse NFT in the transentorhinal cortex

within the temporal lobe (Braak & Braak, 1991). In the middle stages, NFT expand to involve the limbic system, including the amygdala, hippocampus, thalamus, hypothalamus, basal ganglia, and cingulate gyrus (Braak & Braak, 1991). The final stages are characterized by widespread neurodegenerative changes related to continued accumulation of NFT, and NFT continue to spread throughout the neocortex (Braak & Braak, 1991). In its 1997 histopathological diagnostic criteria for AD, the National Institute on Aging (NIA) use the Braak stages as the basis for definitive diagnosis of AD, with greater diagnostic certainty at higher Braak stages (Coleman & Dickson, 1997).

The systematic neurodegeneration of specific brain regions correspond to predictable symptoms in individuals suffering from AD. Before any clinical symptoms of AD are apparent, the disease process has already begun as neurofibrillary tangles begin to appear in the transentorhinal cortex (Braak & Braak, 1991). As pathologies accumulate and spread to the entorhinal cortex, episodic memory becomes slightly impaired because the entorhinal cortex is no longer able to effectively facilitate communication between the hippocampus and the neocortex (Tward et al., 2017; Maass, Berron, Libby, Ranganath, & Düzel 2015). Neurofibrillary tangles become more severe and then spread to the limbic system (including the prefrontal and occipitotemporal cortices); dementia syndrome results with impairments of executive function and spatial visualization respectively (Serrano-Pozo et al., 2011; Tam & Pasternak, 2017). In the final stages of AD, neuronal death continues in brain regions previously affected, while pathologies continue to fan out in the frontal, superolateral, and occipital directions, eventually consuming most of the neocortex and resulting in moderated or severe cognitive decline and motor and sensory impairment (Braak, Alafuzoff, Arzeberger, Kretschmar & Treidici, 2006; Serrano-Pozo et al., 2011).

In addition to understanding the individual regions of the brain affected by AD, understanding how multiple regions function together in networks is critical to gaining insight into the neurological mechanisms behind neuropsychiatric clinical symptoms (Van Dam, Vermeiren, Dekker, Naudé, & De Deyn, 2016). Catani, Dell'Acqua and De Schotten (2013) propose that the limbic system can be divided into three functionally related networks. Memory and spatial orientation are functions of the hippocampal-diencephalic and parahippocampal-retrosplenial network (Catani et al., 2013). The default mode network facilitates attention, introspection and knowledge of self (Catani et al., 2013). Emotion, language, and behavioral inhibition are functions of the temporo-amygdala-orbitofrontal network (Catani et al., 2013).

This network model of neurological functioning explains why multiple brain regions are associated with the neuropsychiatric symptoms of AD. Of the three networks, the temporo-amygdala-orbitofrontal network is most affected in later stages of AD. The temporo-amygdala-orbitofrontal network is also most closely associated with agitated behavioral symptoms (Van Dam et al., 2016). Physically agitated symptoms and aggression are associated with NFT in the orbitofrontal cortex, medial temporal cortex, hippocampus, frontolimbic regions, amygdala, and posterior cingulate (Lai, Chen, Hope, & Esiri, 2010; Poulin, Dautoff, Morris, Barrett, & Dickerson, 2011; Tekin et al., 2001; Trzepacz et al., 2013). While the Braak progression of AD pathology would suggest that neuropsychiatric symptoms such as agitation are a late-stage manifestation of AD, their appearance in early AD is associated with a rapid decline in cognition and may serve as a marker of rapid NFT proliferation (Gallagher, Fischer, & Iaboni, 2017). An understanding of the neuropathological networks underlying agitation in AD may help identify symptom clusters for targeted interventions.

Proposed Etiologies of AD

There is still much debate about the causes of AD. One possible explanation is known as the Amyloid Cascade Hypothesis. In this theory, neuropathological changes in AD begin with abnormal deposits of A β (either through excessive production or inefficient removal), and the presence of the A β damage neurons, result in NFT, and cause AD (Van Dam et al., 2016). This theory is supported by observations that the *presenilin 1* and *2* genes code for a protein involved in processing the amyloid precursor protein, and individuals with this gene are predisposed to inherited AD (Hardy & Selkoe, 2002). The amyloid hypothesis is further supported by observations that NFT can occur independently of A β (as seen in individuals with frontotemporal lobar degeneration with parkinsonism), but A β deposits are always accompanied by NFT (Van Dam et al., 2016; Hutton et al., 1998). Therefore, NFT cannot cause the amyloid cascade in AD, but there is a possibility that A β may cause NFT.

Neuroinflammation is another proposed etiology of AD. The immune cells of the brain (astrocytes and microglia) are responsible for synaptic remodeling, pH balance, blood flow, metabolism, and phagocytosis of damaged tissue (Heneka et al., 2015; Hong et al., 2014; Reed-Geaghan, Savage, Hise, & Landreth, 2009). Chronic neuroinflammation may be triggered by A β , genetic mutations, peripheral inflammation, obesity, or mechanical trauma of the brain (Van Dam et al., 2016). The chronic neuroinflammation activates a cascade of inflammatory molecules causing oxidative stress, scarring, and neuronal damage over time (Heneka et al., 2015). As chronic neuroinflammation has been implicated as a causative mechanism in other psychiatric disorders (Najjar, Pearlman, Alper, Najjar, & Devinsky, 2013) and it is also observed in AD, it is possible that neuroinflammation has a role in the development of AD pathologies.

A wide range of other theories about the pathogenesis have also been proposed. Kozlov, Afonin, Evsyukov, and Bondarenko (2017) and Area-Gomez and Schon (2017) hypothesize that AD progression is the result of mitochondrial dysfunction and resulting metabolic failures. In recognizing the similarities between the systematic spreading of pathologies in AD and in Creutzfeldt-Jakob disease, others view AD as a type of prion disease (Bastian, 2017). The inflammatory phenomena in AD have lead others to propose that AD may be caused by underlying systemic infections such as *Bordetella pertussis*, Herpes Simplex Virus, or even chronic gingivitis (Harris & Harris, 2015; Rubin & Glazer, 2017; Singhrao, Harding, Poole, Kesavalu, & Crean, 2015). Still others implicate metals like lead or aluminum from environmental exposure or endogenous iron dysregulation are key to the pathogenesis of AD (Lee & Freeman, 2014; Lidsky 2014; Peters, Connor, & Meadowcroft, 2015). The lack of consensus and wide variety of theoretical etiologies illustrate the complex nature of AD, and suggest that much further research is needed to unify the variety of possible etiologies of AD.

State of the Science: Agitation in Alzheimer Disease

While impairments in thinking and memory are early symptoms of AD, changes in behavior related to AD are common symptoms as well. Behavioral changes may include apathy, social withdrawal, or agitation (McKhann et al., 2011). Because it is particularly challenging to manage, an increased understanding of agitated behavioral symptoms are a research priority.

Agitation is defined by Cohen-Mansfield and Billig (1986) as a wide range of inappropriate verbalizations or motor activities that are not explained by obvious needs. Agitation is expressed with aggressive and non-aggressive verbalizations and physical behaviors (Cohen-Mansfield & Billig, 1986). Agitation is a very common symptom in AD; it occurs in over 71% of individuals with AD (Hendriks, Smalbrugge, Galindo-Garre, Hertogh, & van der

Steen, 2015; Van der Mussele et al., 2015). Up to 85% of individuals with dementia in long term care facilities demonstrate at least one agitated behavioral symptom, the most common of which is general restlessness (Zuidema, Derksen, Verhey, & Koopsman, 2007). The physical aggression component of agitation becomes more common as dementia impairment increases (Zuidema, de Jonghe, Verhey, & Koopmans, 2009).

Risk Factors for Agitation

Although symptoms of agitation are common in AD, they are not continually experienced by all persons with AD. Symptoms may arise from an unidentified unmet need or without any known cause. By understanding the ways in which situational, psychological, cognitive, and physiological factors coincide with agitated behavior, patterns of agitation become clear and interventions become possible.

Situational factors. Environmental surroundings may contribute to agitated behavior in persons with AD. Excessive noise is considered to be an environmental stressor which may lead to agitation (Ragneskog, Gerdner, Josefsson, & Kihlgren, 1998). While features of the built environmental surroundings such as light, sound, and number of residents in a nursing home have not consistently demonstrated a relationship to agitation, other features of the environment such as social factors may have an effect (Cohen-Mansfield et al., 2012; Zuidema et al., 2009).

Other disruptive situational stressors include activities of daily living or social engagements (Corcoran & Gitlin, 1992). Individuals with cognitive decline may be less capable of handling external stressors, and changes to routine, excess stimulation, or changes to physical surroundings can cause agitation (Smith, Hall, Gerdner, & Buckwalter, 2006). Either excessive stimulation (Livingston et al., 2014) or a lack of stimulation and boredom (Kolanowski et al., 2017) can lead to agitation.

Interpersonal factors such as social engagement and communication impact agitation. The presence of familiar family members may be comforting to persons with dementia and reduce agitated behavioral symptoms (Digby, Lee, & Williams, 2017). Cohen-Mansfield and colleagues (2012) found that engagement with any other person was associated with reduced agitation. Non-therapeutic interpersonal relations between caregivers and patients can result in increased agitation (Ragneskog et al., 1998). Furthermore, when patients become agitated it can cause psychological symptoms in caregivers, resulting in negative communication styles which exacerbate agitation in patients (de Vugt et al., 2004).

Social engagement may also have an indirect effect on agitation. Socialization is important for the wellbeing of older adults, and also for their cognitive health. Social environment might play a role in agitated behavior through its effect on cognitive function because social engagement is protective against cognitive decline (Freeman, Spirgiene, Martin-Khan, & Hirdes, 2017). Similarly, associations between increased social isolation and diminished cognition were demonstrated in a longitudinal study by Bennett, Schneider, Tang, Arnold, and Wilson (2006).

Psychological factors. Psychological disturbances may co-occur with agitated behavioral symptoms in persons with AD. Anxiety is experienced by 18-24% of persons with AD (Borsje et al., 2015). Anxiety has been found to be more common in persons with AD who also have agitated behavioral symptoms, with about one third of those who have frequent agitation also reporting anxiety (Van der Mussele et al., 2015).

Depression is common among individuals with AD; it has been reported in 10 to 42 percent of with persons with AD (Borsje et al., 2015). However, depression is more commonly diagnosed in individuals with vascular dementia than AD (Byers, Yaffe, Covinsky, Friedman, &

Bruce, 2010). While the clinical diagnosis of depression is difficult in persons with dementia or AD, these individuals demonstrate significant correlations between higher levels of depressive symptoms and higher levels of agitation (Chen, Lin, Chen, & Liu, 2014; Volicer, Frijters, & Van der Steen, 2012).

Cognitive function. In persons with AD, cognitive function is inversely related to agitated behavioral symptoms. Steinberg et al. (2006) found agitation was related to advanced dementia severity, and agitation was more common with dementia due to AD. Lovheim, Sandman, Karlsson, and Gustafson (2008) found that the prevalence of agitation was the greatest in those with moderate dementia, conflicting with the findings of Steinberg et al. (2006). In a study of adults with only mild cognitive impairment or early AD, Apostolova (2014) found agitation was most common with the amnesic types of cognitive deficits.

Other cross sectional studies report evidence supporting the inverse correlation between cognitive function and agitated behavioral symptoms. In nursing home residents, frequency of agitated behavioral symptoms increased with severity of cognitive impairment related to AD (Ryu, Katona, Rive, & Livingston, 2005; Veldwijk-Rouwenhorst et al., 2017). Agitation is present, but with low prevalence of 15% in persons with mild cognitive impairment, around 33% with mild dementia, and 45-71% of those with moderate to severe dementia symptoms (Livingston et al., 2017). In a model of antecedents of agitation, Chen and colleagues (2014) found that impaired cognitive function had a direct effect on agitation, as well as an indirect effect on agitation through decreased functional ability and resulting depression.

These findings are echoed with longitudinal studies. Worsening of both cognitive performance and agitated behavioral symptoms over time is seen in populations of nursing home residents (Wetzels, Zuidema, Jansen, Verhey, & Koopmans, 2010), and among community-

dwelling individuals with dementia (Borsje et al., 2015). Other neuropsychological symptoms are common with dementia and worsen over time with agitation, including delusions, aberrant motor behavior and apathy (Borsje et al., 2015). It is possible that there is an interaction between neuropathology, agitation, and other neuropsychological symptoms in AD.

The correlation between agitated behavioral symptoms and cognitive decline has been well reported. However the mechanisms through which cognitive impairment and agitation are related remain unknown. It is unclear the extent to which worsening agitated behaviors are a result of increasing neurodegeneration, or if agitation is the result of other changes that are consequences of diminished cognitive performance. It is clear that as agitated behavioral symptoms become more frequent and severe; the consequences for individuals with AD become more pronounced as well.

Physical factors. Agitation is an expected response to physical discomfort or dysfunction. Agitated behavioral symptoms are seen with a range of physical complaints. Steinberg et al. (2006) found agitation was correlated with medical comorbidity severity. Even relatively minor physical discomforts such as deviations in indoor air temperature are associated with increased frequency of agitated behavioral symptoms (Tartarini, Cooper, Fleming, & Batterham). Non-modifiable physical traits such as male gender, younger age of diagnosis, and apolipoprotein E $\epsilon 4$ (*APOE- $\epsilon 4$*) genotype are associated with higher risk of agitation (Kolanowski et al., 2017; Schutte, Reed, DeCrane & Ersig, 2011). Other physical risk factors for agitation include functional ability, sleep, pain, nutrition, and hearing ability which are examined below.

Sleep. Sleep disturbances are more common in persons with AD than in non-demented older adults (Tractenberg, Singer, & Kaye, 2005). Van der Musselle and colleagues (2015) found

that persons with AD exhibited more frequent and severe neuropsychiatric and behavioral symptoms including disinhibition, impaired emotional control, restlessness, delusions, hallucinations, psychosis, activity disturbances, aggressiveness, diurnal rhythm disturbances, and anxiety with the presence of agitation in than in those without significant agitation. However, in individuals with only mild cognitive impairment, only diurnal rhythm disturbances were related to severity of agitation (Van der Mussele et al., 2015). This finding suggests the possibility that sleep disturbances are a risk factor for agitation early in the AD trajectory.

Pain. Individuals with AD may have challenges in expressing themselves, and may not communicate their experience of pain effectively. Their expression of pain may be demonstrated as agitated behaviors. Volicer and colleagues (2012) found that agitated behavioral symptoms and pain scores in persons with AD are correlated. Pain was found to explain much of the variance in agitated behavioral symptoms in persons with dementia when factors such as dementia severity and functional disability were controlled (Pelletier & Landreville, 2007). Pain may increase agitation directly and indirectly through reduced functional ability and increased depression (Chen et al., 2014). Furthermore, pharmacological treatments for pain result in significant reductions in agitated behaviors (Husebo, Ballard, Cohen-Mansfield, Seifert, & Aarsland, 2014). The relationship between pain and agitated behavioral symptoms illustrate the need to adequately assess and treat pain in people with AD.

Appetite and Nutrition. Dietary factors play an interesting role in the expression of agitated behavioral symptoms in people with AD. Loss of appetite and poor nutritional status are prevalent issues for persons with AD (Kimura, Sugimoto, Niida, Toba, & Sakurai, 2018; dos Santos, Fonseca, Tedrus, & Delbue, 2018). Individuals may have reduced food consumption while experiencing agitation or agitation may be triggered by mealtime routines (Milte, Bradley,

Miller, Farrer & Crotty, 2018). Poor nutritional status is associated with worse cognitive status, functional ability, and agitation in persons with AD (Yildiz, Pekel, Kilic, Tolgay, & Tufan, 2015). Importantly, dietary intake is a modifiable factor that may present an opportunity for targeted interventions toward improving agitated behavioral symptoms.

Hearing loss. Hearing loss is common for all older adults. Estimates of age-related hearing loss range between 2 (Sanders & Gillig, 2010) and 45 percent (Albers et al., 2015) of people over the age of 65 years, and is thought to double in prevalence with every additional 10 years of age. Hearing loss is also known to be a correlate of agitated behavior in institutionalized older adults (Cohen-Mansfield, Billig, Lipson, Rosenthal, & Pawlson, 1990; Vance et al., 2003).

Longitudinal studies have found that hearing loss that is caused by central auditory dysfunction often precedes AD diagnosis (Gates, Anderson, McCurry, Feeney, & Larson, 2011). This suggests the possibility of a shared neurodegenerative process between cognitive decline in AD and impairments in hearing and the interpretation of sounds. Another large longitudinal study found that hearing loss was an independent predictor for the development of dementia when controlling for age, gender, education, *APOE-ε4* allele, and cardiovascular risk factors (Gurgel et al., 2014). Furthermore, adults with hearing loss and dementia experienced a faster rate of cognitive decline than those with dementia and normal hearing (Gurgel et al., 2014).

These findings comport with analysis from a case-control analysis of population level data in Taiwan. Hung et al. (2015) reported that the odds ratio of developing AD was 1.39 for individuals with hearing loss compared to those with normal hearing. However, these analyses did not distinguish central from peripheral hearing loss. The consensus that AD, central auditory processing, executive function, attention and memory are inter-associated suggests that there may be a common mechanism which impacts all of these cognitive domains.

Besides serving as an early warning sign of AD, hearing loss may worsen cognitive processing in AD due to the burden of increase cognitive load with diminished hearing. Because hearing impairment requires the simultaneous use of several cognitive resources like attention and interpretation to decipher speech, it may be more challenging to concurrently accomplish other thought processes. This is clearly demonstrated in situations where noisy backgrounds require more cognitive resources to understand speech, which results in impairments in other cognitive functions such as working memory (Tun, McCoy, & Wingfield, 2009).

The concept of a cognitive resource-allocation framework comports with findings by Wingfield and Grossman (2006). In a review of fMRI data, the authors propose a two-stage hearing comprehension process: First, core elements of a sentence are deciphered and processed sentence in the perisylvian region in cerebral hemisphere; Second, the recruitment of associated brain regions involved in working memory and attention allow comprehension of sentence salience (Wingfield & Grossman, 2006). As older adults lose function of central auditory processing, other areas of the frontal and temporoparietal cortex are recruited to maintain auditory processing and speech comprehension abilities. This model could explain the ability of many older and demented patients to maintain language comprehension while other abilities fail.

To distinguish differences in hearing between normal older adults and those with AD, the two groups were compared with physiological and functional hearing tests. Using verbal (phoneme identification test, word identification test) and nonverbal (environmental sound identification test, identification of melodies from popular music) auditory tests for patients with AD and age-matched controls, Eustache et al. (1995) found that both groups had similar levels of moderate hearing loss. However, the AD group made significantly more errors on all functional

hearing assessments than the controls. The authors report that this discrepancy illustrates problems with executive function and/or attention independent of hearing loss.

Hearing loss may contribute to obstacles in accomplishing activities of daily living, but the effects on an individual's lifestyle can be even farther reaching. One of the most burdensome complications of hearing loss is the inability to understand speech, especially in the presence of background noise. In patients with AD, vocal recognition, gender, and speaker discrimination were impaired compared to healthy, age-matched controls (Hailstone et al., 2011). Hearing loss may contribute to impairments in psychological health because difficulties understanding speech may lead to social isolation, depression and reduced quality of life in some individuals (Niemensivu, Manchaiah, Roine, Kentala, & Sintonen, 2015; Sanders & Gillig, 2010). A qualitative study from the United Kingdom described the social limitations of older adults with hearing impairment. Common themes included the loss of identity, inability to communicate, and social isolation (Bennion & Forshaw, 2013). Because social engagement supports healthy cognitive function, (Freeman et al., 2017; Bennett, et al., 2006), and cognitive function is inversely related to agitation, interventions to protect cognitive function by supporting social engagement with optimized hearing should be explored to avoid agitation.

It is unclear whether sensory impairment from hearing loss directly causes the agitated behavioral symptoms or if a common underlying cause (such as neurodegeneration) is responsible for both the hearing loss as well as the agitated behavioral symptoms. Hearing loss as a predictor of neurodegeneration and AD may be useful for increased surveillance of cognition and early treatment interventions. Hearing loss as independent cause of agitation due to sensory impairment suggests the possibility that interventions to improve communication and optimize hearing ability may ultimately contribute to reduced agitation.

Associated Outcomes

Quality of life for persons with Alzheimer Disease. Individuals with dementia have decreased quality of life (as measured by proxy reports from caregivers and self-report) as levels of agitation increase (Beerens, Zwakhalen, Verbeek, Ruwaard & Hamers, 2013; Hongisto et al., 2015; Livingston et al., 2017). Unfortunately, there is no evidence that quality of life measures improve with many of the interventions aimed at reducing agitation such as increased staffing levels or increased family visits (Livingston et al., 2014; Livingston et al., 2017; Robertson et al., 2017). There is an urgent need to improve quality of life for these individuals, and the possibility that reduced agitated behavioral symptoms can improve quality of life.

Functional status. Impaired functional ability, as measured by performance of activities of daily living, is correlated with agitation (Cohen-Mansfield et al., 2012; Chen et al., 2014). Functional status may also be impacted by the psychological issues such as depression, physical problems such as declining cognition, and environmental considerations including living at home (Martyr, Nelis, & Clare, 2014). The relationship between functional status and these antecedent factors may be moderated by agitated behavior symptoms (Martyr et al., 2014). It has also been suggested that functional ability has an indirect effect on agitation through depression, although a direct effect of functional ability on agitation has not been demonstrated (Chen et al., 2014).

Risk for Admission to caregiving institutions. Many individuals with AD are eventually admitted to long-term care facilities. As agitation increases, the weekly hours of supervision and assistance required also increases significantly (Okura et al., 2011). Caregiver burnout or caregiver distress mediates the relationship between agitated behavioral symptoms and admission to long-term care facilities (Gaugler et al., 2009). Admission to long-term care

facilities is not only financially costly, it also reduces functional and cognitive ability as well as quality of life for residents (Cobo 2014; Foebel et al., 2016).

Exposure to Psychopharmacologic treatment. Persons with AD may be treated with psychoactive medications in an attempt to control or reduce agitated behavioral symptoms. Atypical antipsychotic medications are widely prescribed to treat agitated behavior. As with all medications, adverse effects are possible while taking these drugs. These adverse effects are in especially problematic for older adults. The Food and Drug Administration (2005; 2008) has issued public health advisories related to the increased risk of death when antipsychotic drugs are used in a population of older adults with dementia. Despite guidelines designed to reduce the use of these drugs, prevalence of their use remains between 40 and 68 percent of institutionalized people with dementia (Mitka, 2012; Foebel et al., 2016).

While atypical antipsychotic medications such as aripiprazole, quetiapine, risperidone and olanzapine significantly reduce agitated behavioral symptoms, they also have significant risks of adverse effects (Ma et al., 2014). Adverse effects range from minor issues such as edema and gait abnormalities to severe problems of somnolence, urinary tract infections, extrapyramidal symptoms, adverse cerebrovascular event and even death (Ma et al., 2014). The risks of cardiovascular events and death were increased with medication dose and duration of use (Schneider et al., 2006).

Besides the immediate adverse effects of antipsychotic drugs, long-term effects are also seen. Individuals who are treated with antipsychotic medications were found to have declines in functional ability and cognition compared to those who were not medicated (Foebel et al., 2016). Since cognitive decline is associated with worsening agitated behavioral symptoms, the long-

term use of antipsychotic medications and the associated cognitive decline may contribute to worse agitation and the need for even more medication in long term use.

Other psychoactive medications have been tested to treat agitated behaviors in persons with AD. Antidepressant drugs have been used for the treatment of agitated behavioral symptoms in persons with AD even without depression. A Cochrane review found a significant improvement in agitation after administration of selective serotonin reuptake inhibitors sertraline and citalopram, although not all trials have confirmed this finding (Seitz et al., 2011). While generally considered safer than antipsychotic medications, antidepressants increase the risk of falls, electrolyte imbalances or gastrointestinal bleeding especially in older adults (Seitz et al., 2011).

Anxiety is common in individuals with AD, and anxiety medication may be used to treat agitated behavioral symptoms in these individuals (Borsje et al., 2015). Anxiolytic agents are effective in treating agitation with short-term use, but can cause cognitive impairment, balance problems, and short-term memory impairment (Antonsdottir, Smith, Keltz, & Porsteinsson, 2015). Furthermore, long-term use of benzodiazepines are strongly associated with increased risk of development of dementia (Takada, Fujimoto, & Hosomi; 2016).

Exposure to Physical restraint. While not as prevalent as the use of antipsychotic medications, physical restraints are widely used to control agitated behavioral symptoms in persons with AD. It is estimated that physical restraints are used to manage agitated behavioral symptoms in 20 to 31 percent of persons with AD and agitated behavioral symptoms in nursing home settings (Foebel et al., 2016). The use of physical restraint is also likely to contribute to additional psychological distress (Werner, Cohen-Mansfield, Braun, & Marx, 1989).

Following a similar trend to antipsychotic medication interventions, individuals who are physically restrained were found to have declines in functional ability and cognition compared to those who were not restrained, and also compared to those who received only antipsychotic medications (Foebel et al., 2016). The functional and cognitive declines were the worst in nursing home residents who were both physically restrained and medicated, suggesting an additive effect (Foebel et al., 2016). It is possible, however, that cognitive and functional declines were greater in this population due to the advancing disease process itself rather than as a direct response to the physical restraint and medication interventions as no random assignment to groups were made in Foebel's retrospective observational study.

Caregiver Burden. Agitated behavioral symptoms are not only one of the most prevalent symptoms in AD, they are also one of the most distressing symptoms to caregivers (Chiao et al., 2015; Fauth & Gibbons, 2014). Caregiver burnout is a problem for family members who care for persons with AD, and is associated with immune dysfunction, increased risk of stroke, and increased pain (Fonareva & Oken, 2014; Hong et al., 2016; Ivey et al., 2017).

In the hospital setting, nurses and other professional caregivers may not respond adequately to the care requirements of persons with AD and agitated behavioral symptoms. In response to these challenging behaviors, nurses may react with avoidance or depersonalization, ignoring these patients and providing only basic task-oriented care without compassion (Digby et al., 2017). Healthcare Providers may respond to aggression or agitated behavioral symptoms with physical force or chemical restraint (Nilsson, Rasmussen, & Edvardsson, 2015). When patients with dementia are resistant to care, nurses may become angry or exasperated (Nilsson et al., 2015). In some instances, nurses may even dehumanize these individuals resulting in the patients being treated cruelly with shouting, mockery or with derogatory remarks (Griffiths et al.,

2014; Digby et al., 2017). Digby and colleagues (2017) suggest that these unprofessional caregiving behaviors are the result of nurses' attempts to gain control of patient behaviors, a lack of understanding or training about AD, and a lack of adequate time to look for reasons for agitated behavioral symptoms. In situations where nurses are unable to provide safe and dignified care to persons with AD who have agitated behavioral symptoms, is not only unsafe for patients but also dissatisfying to staff.

An extreme expression of caregiver burnout is the abuse or neglect of persons with AD. Older people with dementia symptoms are at a greater risk for verbal and physical abuse in the community and also in institutional settings compared to the elderly population in general (Boye & Yan, 2016). Elder abuse was found to be predicted by caregiver factors such as depression or stress, and patient factors including functional impairment, neuropsychiatric symptoms, and dementia symptoms (Cooper et al., 2010; Pérez-Rojo et al., 2009; VandeWeerd et al., 2013). Physical abuse of persons with AD is often triggered by disruptive behaviors such as agitation, resistances to care, and aggression (Cooper et al., 2010; Pérez-Rojo et al., 2009; VandeWeerd et al., 2013).

Gaps in the Literature

As a whole, the current body of evidence surrounding agitated behavioral symptoms in AD provides evidence that (1) current interventions to improve agitated behavioral symptoms in persons with AD are ineffective overall, (2) many possible risk factors for agitation have been identified, and (3) outcomes for unresolved agitated behavioral symptoms are dire.

Interventions with some evidence of improvement to agitated behavioral symptoms include environmental modifications and music therapy, communication training for caregivers, physical exercise, and some medications. Light therapy, staff training to encourage social

interaction or exercise, and aromatherapy interventions are not efficacious. Since pharmacological interventions carry high risks of dangerous adverse events and the effects of currently described nonpharmacological interventions are limited, there is a need to develop new interventions to improve agitated behavioral symptoms in persons with AD through careful evaluation of risks for and antecedents to agitated behaviors.

Cognitive decline is a key risk factor for agitation, and cognitive function may moderate the effects of other protective factors such as social interaction and physical exercise. It is unclear the extent to which worsening agitated behaviors and cognitive decline are both the result of increasing neurodegeneration, or if agitated behavioral symptoms are a direct response to increasingly impaired cognition. Furthermore, there is no evidence to determine if supporting healthy cognition can improve cognitive behavioral symptoms or vice versa.

While many situational, psychological, and physiologic factors have been found to be correlated with agitated behavioral symptoms, there is limited evidence to determine if these factors are causative or simply correlated. Risk factors for agitation such as unidentified pain, insufficient sleep, inappropriate level of stimulation, or untreated anxiety or depression merit further exploration. Interventions to identify and treat pain, improve sleep cycles, and provide appropriate stimulation may provide additional opportunities to improve agitated behavioral symptoms.

Hearing loss is another important risk factor for agitated behavioral symptoms. While some hearing loss may be an unavoidable result of neurodegeneration in AD, the effects of hearing loss are immense. Interventions to examine the possibility of improving agitation directly through improvement of hearing are needed. Additionally, interventions to improve communication for those with hearing impairment may improve agitation indirectly through

avoidance of social isolation and improved cognition. More work is needed to investigate these promising interventions.

The consequences of continuous agitated behavioral symptoms include diminished quality of life, caregiver burnout, chemical or physical restraint, low quality hospital care, early institutionalization, abuse or neglect, and adverse drug effects including death. To avoid these outcomes, better interventions for agitated behavioral symptoms are urgently needed. By clarifying the relationship of antecedents and risk factors of agitated behavioral symptoms, opportunities for effective interventions will become clear.

Conceptual Challenges

Dementia and Alzheimer disease. The first conceptual challenge in researching the phenomenon of agitated behavioral symptoms in persons with AD is defining the population. The definition of AD has undergone numerous revisions. In 1984, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) agreed on criteria to define the clinical diagnosis of AD based on neuropsychiatric tests and medical history (McKhann et al., 1984). As knowledge about the AD neurodegenerative process and other pathophysiological processes with similar symptom presentations grew, new diagnostic criteria for AD were created (McKhann et al., 2011).

The currently accepted definition of AD, known as the NINCDS-ADRDA criteria described by McKhann et al., 2011, includes a broad definition for dementia regardless of etiology. This general definition of dementia includes cognitive or behavioral symptoms based on five criteria: symptoms that impede usual activities; are a decline from an individual's baseline functioning; cannot be attributed to another psychiatric disorder; are observed through

subjective report as well as objective measures; and involve at least two cognitive domains such as memory, reasoning, visuospatial abilities, language, or personality. When these symptoms are present, but mild enough that they do not interfere with usual activities, Mild Cognitive Impairment (MCI) is diagnosed. While MCI may be considered an early presentation of AD, it is not definitive that MCI will progress to AD.

Dementia occurring secondary to AD is further categorized as probable, possible, and “Probable or possible AD dementia with evidence of AD pathophysiological process” (McKhann et al., 2011, p. 265). These further delineations depend on a patient history with insidious symptom onset with initial presentation of memory deficits (amnestic presentation), or language, visuospatial, and executive deficits (nonamnestic presentation). AD is not diagnosed if an individual has a history of cerebrovascular disease or features of other types of dementia such as Lewy body or frontotemporal dementia. The diagnosis of AD may be made with increased level of certainty in the presence of biomarkers or genes.

With these stringent diagnostic criteria and the requirement of knowing each individual’s history and presentation, it is not surprising that so much research with older adults who experience cognitive decline does not attempt to differentiate dementia caused by AD from other dementias. Even when Alzheimer diagnosis status is known for some participants, researchers may combine all individuals with dementia symptoms in analysis.

Even the more general term, “dementia,” does not have a universally agreed upon definition. The World Health Organization International Classification of Disease (ICD-10) has categorized dementia as a mental and behavioral disorder (World Health Organization, 2004), and further defines dementia on the basis of its etiology. The American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM) removed the term dementia from

its fifth edition, instead referring to these symptoms as a neurocognitive disorder (American Psychiatric Association, 2013).

Some authors have argued that the distinction between different types of dementia in older adults is futile. There is a high prevalence of “mixed dementia” arising from a combination of vascular and AD pathologies, with an increased risk of clinical dementia symptoms with additional pathologies (Schneider, Arvanitakis, Bang, & Bennett, 2007). There is also poor correlation between clinical diagnosis and neuropathological findings seen in postmortem brain examinations (Schneider, Arvanitakis, Leurgans, & Bennett, 2009). Despite these imperfections, distinctions between different etiologies causing dementia are important to avoid extrapolating findings from one type of dementia to all types.

Operationalization of AD or other dementias has taken various forms in the literature. In the absence of a formal diagnosis, scores on neuropsychological assessments are often used to label dementia and quantify severity of cognitive impairment. The wide variety of tools available makes comparisons across studies more difficult. While the benefit of these assessments is that the numerical scores allow for easy analysis and they do not require lengthy examination or expert input, tools are often limited in diagnostic accuracy in all populations and may only represent the cognitive domain of dementia without regard to impact on functional ability (Ritchie, Terrera, & Quinn, 2015).

Agitation. Lack of conceptual clarity is a problem in the literature describing agitation in AD. Cohen-Mansfield and Billig (1986) consider four components of agitation including physically aggressive behavior, physically non-aggressive behavior, verbally agitated behavior, and hiding or hoarding. The agitated behaviors are deemed socially inappropriate because: “It may be abusive or aggressive toward self or others; it may be appropriate behavior performed

with inappropriate frequency; and it may be inappropriate according to social standards for the specific situation” (Cohen-Mansfield & Billig, 1986, p. 712). Aggression refers to destructive behaviors directly at people, oneself, or objects (Cohen-Mansfield, Marx, & Rosenthal, 1989). Cohen-Mansfield (2003) explains that agitated behavioral symptoms may be determined by an observer, are not necessarily disruptive, and occur in individuals both with and without dementia.

Other definitions of agitation have been proposed. The DSM-5 defines psychomotor agitation as excessive motor activity associated with a feeling of inner tension where the activity is usually nonproductive and repetitious and consists of behaviors such as pacing, fidgeting, wringing of the hands, pulling of clothes, and inability to sit still. (American Psychiatric Association, 2013). This definition of agitation describes the non-aggressive behavioral aspect of agitation described by Cohen-Mansfield and Billig (1986), but does not address aggressive or verbal behaviors. The DSM-5 definition of agitation also presents research challenges because it is not easy to observe feelings of inner tension, and may be difficult to ascertain these feelings in persons with AD due to their communication limitations.

Agitation has also been described as a set of observable behaviors that demonstrate an unpleasant state of excitement and do not respond to interventions to remove internal or external stimuli (Hurley et al., 1999). Hurley and associates (1999) further explain that agitation is a state that is experienced by an individual who is alone, while the same behaviors in the presence of caregivers would be termed “resistance to care.” Examples of these behaviors include pacing and repetitive movements or vocalizations. This definition is problematic because, by definition, it cannot be improved through intervention. Hurley’s (1999) definition assumes that all agitated behaviors that occur in the presence of caregivers represent a rejection of care, although the

individual may not realize they are rejecting care. This definition also omits aggressive behaviors toward self, others or objects.

Kong (2005) describes a conceptual framework through which agitation can be understood, and emphasizes that conditions preceding the agitation must be explored. While the definition of agitation proposed by Cohen-Mansfield and Billig (1986) indicates that agitation is the presence of inappropriate behavior in the absence of need, Kong (2005) emphasizes the importance of assuring that physical needs are not the cause of the agitated behavioral symptoms. Unmet physical or psychological needs such as pain or sleep deficits are likely to cause a person with dementia to express this need through motor activity or verbalizations.

Although Cohen-Mansfield and Billig created the most widely-used definition of agitation in 1986, there is no universal acceptance of this definition. Agitation describes such a wide range of behavioral symptoms that it overlaps several related concepts. For example, agitation includes aggressive behaviors but aggression is not always present in agitated behaviors such as pacing (Cummings et al., 2015). Other concepts which are closely related to agitation including restlessness, aggression, and disturbing behaviors are often included in the conceptual definition of agitation (Kong, 2005). Concepts which may be considered as a part of agitation such as aberrant motor behaviors including wandering or fighting (Fauth & Gibbons, 2014) and inappropriate verbalizations such as screaming or ceaseless talking (von Gunten, Favre, Gurtner, & Abderhalden, 2011) are often studied in isolation to other aspects of agitation.

The construct of agitation contains many different symptoms, making it a challenging target to measure (Kolanowski et al., 2016). Lack of agreement on the conceptual definition of agitation has resulted in the concept being operationalized with different tools in different studies. Commonly used tools include the Cohen-Mansfield Agitation Inventory (Cohen-

Mansfield *et al.*, 1989), Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994), or Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD; Reisberg *et al.*, 1987; De Deyn & Wirshing, 2001). These different instruments make cross study comparisons difficult.

Because of a lack of agreement about the definition of agitation, an Agitation Definition Work Group was formed by the International Psychogeriatric Association and 928 participants responded to questionnaires to reach consensus. As a result, a standard definition of agitation was created. "Agitation was defined broadly as: (1) occurring in patients with a cognitive impairment or dementia syndrome; (2) exhibiting behavior consistent with emotional distress; (3) manifesting excessive motor activity, verbal aggression, or physical aggression; and (4) evidencing behaviors that cause excess disability and are not solely attributable to another disorder (psychiatric, medical, or substance-related)," (Cummings *et al.*, 2015, p. 7). This definition adds to that which was proposed by Cohen-Mansfield (1986) by the explanation that agitation in persons with cognitive impairment or dementia may differ in etiology and treatment than agitation which is seen in other conditions. The "unmet needs" aspect of the definition is reframed as "an excessive response." This definition of agitation is also unique in its recognition that the behavior interferes with normal or expected functioning.

While it is yet to be seen if this new definition will replace the traditional conceptual definitions of agitated behavioral symptoms, its creation demonstrates the efforts that have gone into creating conceptual clarity from the heterogeneity in previous definitions. Further work will be needed to determine the extent to which extant tools are valid to measure agitation as it has been conceptualized above.

Nursing Theory: The Theory of Unpleasant Symptoms

Although the experience of agitated behavioral symptoms in persons with AD is very common, interventions to reduce agitated behavioral symptoms are still unreliable. The consequences of untreated agitated behavioral symptoms are severe, ranging from diminished quality of life to abuse and even death. To better understand agitated behavioral symptoms in person with AD, the phenomenon has been conceptualized with theories like the Need-driven Dementia-compromised Behavior (NDB) model (Algase et al., 1996) and the Progressively Lowered Stress Threshold (PLST) model (Hall & Buckwalter, 1987).

The NDB model proposes that background factors (such as neurological status, health status, premorbid characteristics) and proximal factors (including physical or psychosocial needs and environment) result in disruptive behavioral symptoms related to dementia (Algase et al., 1996). The PLST model is based on the idea that the disruptive behavioral symptoms seen in persons with dementia are a response to overwhelming stress on the patient, and disease progression results in lower doses of the triggering events resulting in the stress response (Hall & Buckwalter, 1987). These models have been helpful in directing environment interventions to minimize behavioral disruptions; however these two models are limited because they lack explicit attention to functional performance as a secondary outcome beyond disruptive behavioral symptoms.

To understand the relationship between these environmental stressors, needs, behavioral symptoms, and their effects on an individual's functional performance, another model is needed. Numerous situational, psychological and physical risk factors for agitated behavioral symptoms have been identified, but their relationship to agitation is complex and not fully understood. A framework is needed to organize these risks, understand their relationship to agitated behavioral

symptoms, and identify opportunities for future interventions. The TOUS is a good fit to model these relationships.

The Theory of Unpleasant Symptoms

The middle-range TOUS was originally developed by Lenz and colleagues to better understand the symptoms of fatigue and dyspnea in the populations of women in child birth and individuals with lung disease (1995; Figure 1). Despite the differences in these symptoms and populations, concepts that were common to both symptoms experiences were identified and defined in a way that could be extrapolated to other unpleasant symptom experiences (Lenz et al., 1995). The TOUS was later updated to recognize the coexistence and associations between multiple symptoms (Lenz et al., 1997; Figure 2). The updated theory also considers the role of performance outcomes in further influencing the symptom experience and antecedent factors (Lenz et al., 1997).

Evaluation of TOUS

The TOUS can be critiqued through Fawcett and DeSanto-Madeya's theory evaluation criteria including theory scope, context, and content (2013). The scope of the theory is constrained to the middle-range nursing phenomenon since its theoretical concepts are more concrete and specific than the abstract and broad concepts of grand theories. The TOUS was developed with the goal of providing a guide for nursing theory and practice; the concepts and relational statements of the TOUS are precisely defined (Lenz et al., 1995).

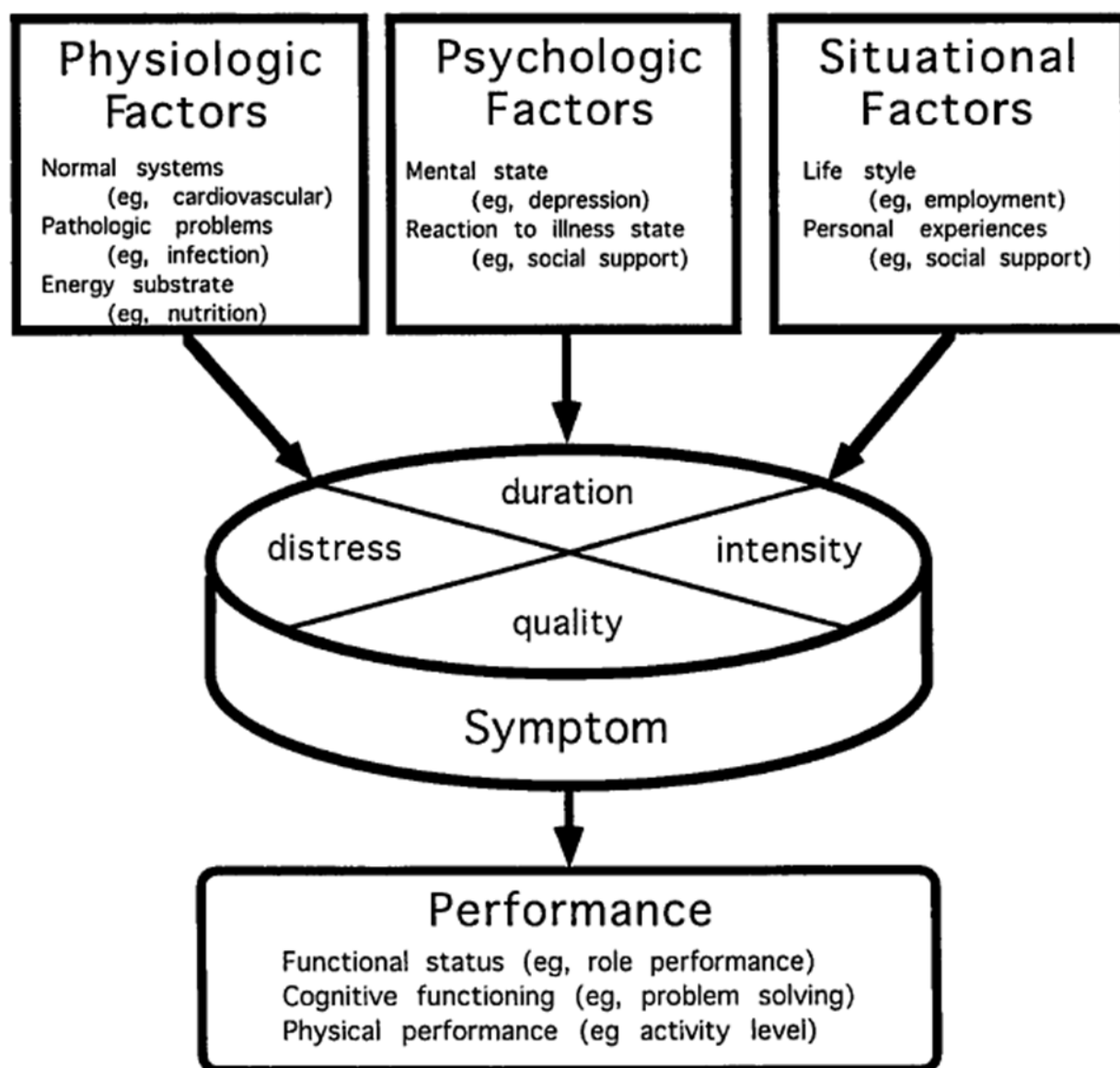


Figure 1. Original Theory of Unpleasant Symptoms (Lenz et al., 1995)

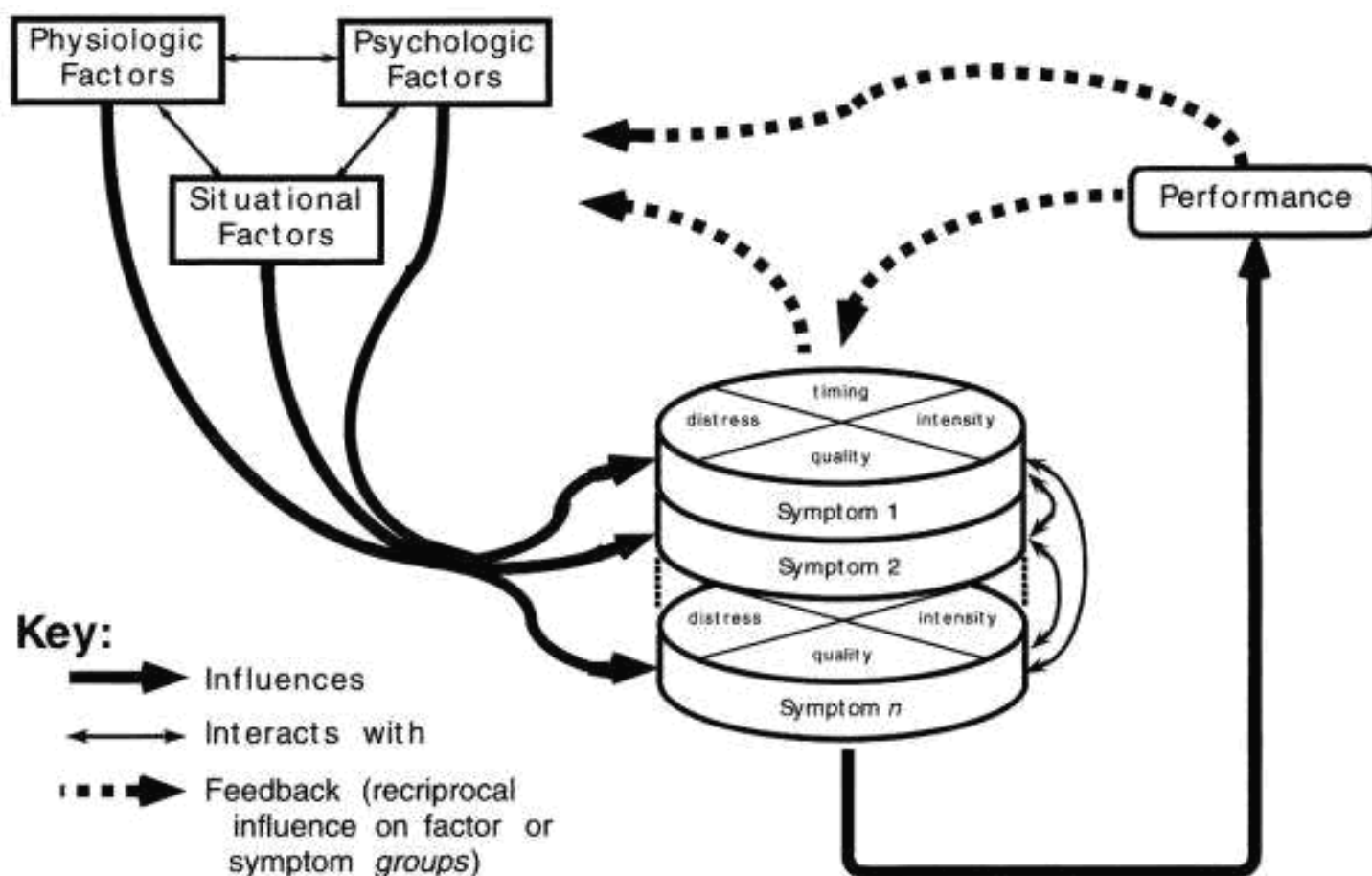


Figure 2. Updated Theory of Unpleasant Symptoms (Lenz et al., 1997)

The context of the nursing theory (its relation to nursing's metaparadigm, philosophical claims, conceptual model, and fit within previously developed nursing knowledge) places it squarely within the nursing disciplinary perspective. Nursing's metaparadigm concepts of nursing, human beings, health, and the environment are each represented (Fawcett & DeSanto-Madeya, 2013). The concept of health is represented in the symptom experience, and antecedent health factors which influence symptoms (Lenz et al., 1995). Human beings and environment are represented through the antecedent factors of social and physical environment (Lenz et al.,

1995). Nursing is indirectly related to the model itself, but Lenz et al. (1997) note that the TOUS is useful in developing preventative (nursing) interventions to alleviate symptoms. Although philosophical claims of the TOUS are not explicitly stated, the updated TOUS reflects the reciprocal interaction world view (Lee, Vincent, & Finnegan, 2017). The patient is a holistic being who presents symptoms which are influenced by environmental factors (Lenz et al., 1997). The environment and multiple symptoms have a multiplicative effect on the symptom experience and performance outcomes; these features create a feedback loop through which symptoms are reinforced through performance factors (Lenz et al., 1997).

The content of the TOUS is evaluated on the basis of its significance, internal consistency, parsimony, testability, and empirical and pragmatic adequacy (Fawcett & DeSanto-Madeya, 2013). The theory is highly significant to nursing as demonstrated by its attention to the metaparadigm concepts of interest to nursing and its development process through clinical nursing observations and review of extant nursing literature (Lenz et al., 1995). The internal consistency of the TOUS is demonstrated in the clear and concise definitions of theoretical concepts and provision of examples of each (Lenz et al., 1995). There is a minor problem with semantic consistency in the interchangeable use of the terms symptoms/symptom experience and functional activities/functional performance/functional status, and performance/performance outcomes (Lee, Vincent, & Finnegan, 2017). Overall, the interchangeable use of these terms does not interfere with the understanding of relational concepts, and allows users of the TOUS the flexibility to define these terms to provide the greatest utility to their own phenomena of interest. The TOUS is testable; it has been used as the conceptual model in at least 152 different studies many of which found evidence to support the TOUS empirical and pragmatic adequacy (Lee, Vincent, & Finnegan, 2017).

This model is particularly well-suited to the study of the determinants of agitated behavioral symptoms in persons with AD because the TOUS was developed with the recognition that multiple symptoms often occur together and may exacerbate one another. The theory considers antecedents to symptoms such as physiological factors, psychological factors and situational factors; describes the symptoms themselves in terms of distress, duration, quality, and intensity; and considers the outcome of beyond just the presence or absence of symptoms including functional abilities (activities of daily living, role performance) and cognitive performance (concentration, problem solving). The inclusion of performance variables as an outcome is consistent with the conceptual definition of agitation described by Cummings and colleagues (2015).

Variables within Theory of Unpleasant Symptoms Framework

Symptom. The concept of agitation fits into the TOUS model as a symptom defined by its distress, duration, intensity, and quality. In this study, agitation will be defined as behaviors consistent with emotional distress, excessive motor activities, and verbal or physical aggression which negatively impact an individual or others around them and which are not solely attributable to another disorder (Cohen-Mansfield, 1986; Cummings et al., 2015).

Based on the model, the symptom of agitation will be impacted by the combined effects of physiological, psychological, and situational factors. The agitated behavioral symptoms will also have an effect on performance including quality of life and functional status. The relationship between agitation and other AD-related behavioral symptoms will be described.

Other behavioral symptoms often coincide with agitation in persons with AD. Symptoms of apathy, delusions, disinhibition, elation, hallucinations, and sleep disorders will also be examined. The TOUS predicts that these AD-related behavioral symptoms will also be impacted

by physiological, psychological, and situational factors. The AD-related behavioral symptoms will also have an effect on the performance outcomes of quality of life and functional status. The relationship between AD-related behavioral symptoms and agitation will also be examined.

Antecedent factors. The three categories of agitation-causing variables include situational, psychological, and physical factors. Not only are these factors thought to influence agitated behavioral symptoms, their relationships with each other are also considered. Additionally, the antecedent factors will have an independent effect on performances outcomes.

Situational factors. Situational factors influencing agitation include environmental influences and interpersonal factors. In the proposed study, situational factors will include the physical and social environment. The situational factor construct will be studied in terms of three effects: its correlation with physical and psychological factors; its effect on agitation; and its effect on performance outcomes.

Psychological factors. Psychological factors will be defined as anxiety and depression. In the proposed study, the psychological factor construct will be studied in terms of three effects: its correlation with physical and situational factors; its effect on agitation and other AD-related behavioral symptoms; and its effect on performance outcomes.

Physiologic factors. Physical factors will be defined as comorbidities, pain, nutritional status, hearing, cognitive impairment (as a marker of AD stage of progression), and fatigue. In the proposed study, the physiologic factor construct will be studied in terms of three effects: its correlation with physical and situational factors; its effect on agitation and other AD-related behavioral symptoms; and its effect on performance outcomes.

Performance. For the purposes of the present study, the performance construct will be defined as functional status and quality of life. As indicated in the TOUS, performance will be

studied as a direct and indirect outcome of situational, psychological, and physical factors; it will also be studied as a direct effect of agitation and other AD-related behavioral symptoms.

Model. By considering the compounding effects of multiple symptoms that occur simultaneously, it is clear how other symptoms which are common in aging such as depression, social isolation, pain, hearing loss, or sleep difficulties may exacerbate the symptom of agitation and ultimately diminish quality of life and functional performance. The TOUS model helps clarify and organize the seemingly unpredictable nature of agitation by providing a clear framework for understanding the symptom, its causes, and its effects on performance.

Performance is the outcome variable of this theory. Performance may include things like role performance, activity level, or problem solving. These factors together may influence quality of life overall. The resulting decrease in performance and function may act through a feedback loop to perpetuate the cognitive decline symptom and exacerbate situational, psychological, and physiological risk factors for even further cognitive decline.

From this model it can be deduced that if the symptoms of agitation and other AD-related behavioral symptoms increase, then functional performance will decrease. The model also visually depicts that a greater level of physiological impairment from AD or other dementias contributes to an increased frequency of agitation and other AD-related behavioral symptoms and ultimately further decrease functional performance. Lastly, the resulting decrease in functional performance may act through a feedback loop to perpetuate the agitation symptom and exacerbate psychological, situational, and physiological risk factors for even further agitation. The TOUS provides a framework of proposed relationships that can be empirically tested.

For the purposes of the present study, the simplified original version of the TOUS (Lenz et al., 1995) will guide analyses. The correlations between antecedent factors will also be considered as described in the updated TOUS (Lenz et al., 1997). Although it is clear that feedback mechanisms described in the updated TOUS will cause iterative, reciprocal effects from performance to symptoms and antecedent factors over time, only the direct paths will be analyzed. Inclusion of reciprocal paths within a single model would preclude the possibility of path analyses. Furthermore, cross sectional data provides only a snapshot in time: further study of longitudinal changes over time is needed to evaluate the feedback mechanisms described in the updated TOUS by reversing the model and considering functional performance and agitation at an early time point the predictors of later declines in antecedent factors.

Chapter 2 Conclusion

All older adults should look forward to the experience of aging and the ability to live their optimal quality of life in a safe and supportive environment. Unfortunately, persons with AD who experience agitated behavioral symptoms may be unable to achieve their maximum potential functional performance and quality of life (Beerens, et al., 2013; Hongisto et al., 2015; VandeWeerd et al., 2013). Moreover, agitated behavioral symptoms may result in strained relations with caregivers, early admission to residential institutions, administration of drugs with dangerous side effects, physical restraint, and even elder abuse (Gaugler et al., 2009; Ma et al., 2014; VandeWeerd et al., 2013). Current nonpharmacological interventions are unreliable or unsafe (Livingston et al., 2017; Foebel et al., 2016). There is evidence that agitated behavioral symptoms are related to a number of situational, psychological, and physiological factors, however the nature of their relationship to agitation are still unclear. There is a critical need for

research guided by theory such as the TOUS to organize these risks and outcomes, predict relationships, and identify opportunities for intervention.

In conclusion, the TOUS provides a clear and comprehensive framework for understanding the phenomenon of agitated behavioral symptoms in persons with AD. Knowledge generated through the TOUS about agitation and cognitive decline has the potential to improve care for older adults with cognitive impairments and also to contribute to nursing knowledge. As long as a cure for AD is unattainable, a great need exists to improve the care of agitated behavioral symptoms in persons with AD.

CHAPTER 3: METHODS

Methods

Study Design

This dissertation's purpose is to test a model of predictors and outcomes of agitated behavioral symptoms in persons with AD. This study used a descriptive, correlational design with cross-sectional data. The specific aims of the study were tested theoretically and empirically. Aim 1 seeks to describe the phenomenon of agitated behavioral symptoms in persons with AD within the Theory of Unpleasant Symptoms. Aim 1 will be assessed by the degree to which the path model calculated from the data matches the substructured model guided by the TOUS, and adequately represents all of the expected theoretical concepts. Aims 2 and 3 seek to examine the relationships between situation, psychological state, and physical conditions on agitation and functional status outcomes. These aims will be empirically tested to determine the presences, strength and direction of relationships between variables of interest in the model to evaluate the degree to which relationships hypothesized in the TOUS are supported by the data.

Setting

This study analyzes data from previous studies of persons with AD. The original studies examined genetic and environmental determinants of functional abilities, cognition and behavioral symptoms in persons with AD. In the parent studies, participants were recruited from community and nursing home settings in the Midwest (Schutte, Maas, & Buckwalter, 2003; Schutte et al., 2011).

Sample

Parent studies used convenience sampling to identify nursing home facilities and community-dwelling individuals with AD from which all eligible participants were invited to join the studies. Although some parent studies collected data from participants at multiple time points, only baseline data for all participants were included in the present analysis. Data from parent studies yielded a sample size of up to 110 participants. Some instruments were not used across all studies, so sample sizes for individual measures varied between 5 and 110 participants. A minimum sample of 48 participants was included in each variable in the model, with other instruments evaluated separately. The *G*Power* analysis found that a sample of 48 participants achieves a statistical power of 0.84 in detecting a moderate effect size ($f^2 = 0.15$) for a one-tailed α level of 0.05 in analyses of multiple regression with four predictors (Faul, Erdfelder, Lang, & Buchner, 2007).

Inclusion criteria. Subjects were eligible to participate if they met the NINCDS-ADRDA criteria for possible or probable AD, were over the age of 21 years, were fluent in English, and had the consent of a family member for participation.

Exclusion Criteria. Persons not meeting the inclusion criteria were excluded.

Procedures

All study procedures from the parent studies were approved by Institutional Review Boards. Approval by the Institutional Review Board at Wayne State University was obtained before data analysis began. Since the data for the dissertation research had already been collected, risks for participants were minimal. Risks included the loss of privacy if protected health information was compromised. This risk was minimized by accessing only de-identified

data safely stored in password protected electronics or hard copies of data assessment forms stored in locked file cabinets in a locked office.

Recruitment. In the community, participants were recruited through their caregivers. In nursing home settings, administrators at each facility mailed letters describing the study to legally authorized representative of eligible participants (Schutte et al., 2011). These representatives were asked to indicate if they were interested in learning more about participation in the study from the research team. Interested families were contacted by telephone to describe the research and obtain informed consent. From the nursing home setting, an average of 51% of eligible individuals chose to participate (Schutte et al., 2011).

Data Collection. Data were collected from chart review, questionnaires administered to the participants, and family informant interview. For some data, repeated measures were collected for participants at various time points (Schutte et al., 2011). To assure interrater reliability, functional ability and cognitive impairment assessments were measured by two members of the research team simultaneously for the first three participants at each new facility, with an intraclass correlation of greater than 0.75 for all measures (Schutte et al., 2011). Any discrepancies that arose were discussed and resolved by consensus (Schutte et al., 2011).

Measures

In the following section, descriptions of instruments used to measure each theoretical concept are described. The instruments are organized by the theoretical concept measured. In cases where subscales of an instrument are used, the details of the instrument are described within the first variable measured and the subscale is listed under the applicable theoretical concept. The theoretical concept, variable, and measures are summarized in Table 1.

Table 1. *Theoretical Concepts, Definitions, and Measures*

Theoretical Term	<i>Definition</i>	Conceptual Term	<i>Definition</i>	Empirical measures
Situational antecedent factors	<i>"Aspects of the social and physical environment that may ... include employment status, marital and family status, social support... noise, light, and air quality" (Lenz et al., p. 18-19)</i>	Social Environment	<i>Opportunities for social engagement and caregiver perceptions of burden.</i>	Nursing Unit Rating Scale Zarit Burden Interview Score MBPC Memory and Behavior Caregiver reaction subscale MBPC ADL Caregiver reaction NPI Occupational disruptiveness
		Physical Environment	<i>The built environment and the degree to which it supports optimal functioning.</i>	Community or Institutional Residence Ambiance Scale Therapeutic Environment Screening Survey
Psychological antecedent factors	<i>An individual's "mental state or mood, affective reaction to illness, and degree of uncertainty and knowledge about the symptoms" (Lenz et al., 1997, p. 18).</i>	Mood	<i>The affective presentation of persons with AD.</i>	NPI Depression subscale NPI Anxiety subscale NPI Apathy subscale
		Psychosis	<i>Beliefs or sensory experiences which are not consistent with reality.</i>	NPI Delusions subscale NPI Hallucinations subscale
		Elevated Behavior	<i>Dysregulated actions or emotions.</i>	NPI Elation subscale NPI Disinhibition subscale NPI Motor subscale NPI Sleep subscale NPI Irritability subscale ADAS Non-cognitive Behavioral FAC Inappropriate behavior subscale

Table 1. *Theoretical Concepts, Definitions, and Measures* (continued)

Theoretical Term	<i>Definition</i>	Conceptual Term	<i>Definition</i>	Empirical measures
Physiologic antecedent factors	<i>Physiologic factors include the functioning of body systems, pathologies, nutrition, and energy level (Lenz et al., 1997)</i>	Comorbid Diseases	<i>Additional concurrent disease states.</i>	Cumulative Illness Rating Scale-Geriatrics
		Pain	<i>Physical discomfort.</i>	Pain Assessment in Advanced Dementia
		Nutritional Status	<i>Decreased nutritional intake or decreased desire for food.</i>	Mini Nutritional Assessment NPI Appetite subscale
		Hearing Impairment	<i>Reduced hearing ability.</i>	Hearing Inventory Screening form Long Term Care Minimum Data Set
		AD-related cognitive impairment	<i>Diminished cognition in any domain of memory, attention, or problem-solving.</i>	Mini Mental State Exam Severe Impairment Battery ADAS Cognitive subscale MBPC Memory Behaviors subscale FAC Cognitive Status subscale
Symptom: Agitation	<i>The "perceived indicators of change in normal functioning... they are the red flags of threats to health" (Lenz et al., 1995, p. 146).</i>	Agitation	<i>Behaviors consistent with emotional distress, excessive motor activities, and verbal or physical aggression which negatively impact an individual or others around them and are not solely attributable to another disorder (Cohen-Mansfield, 1986; Cummings et al., 2015).</i>	Cohen-Mansfield Agitation Inventory FAC Agitation subscale NPI Agitation subscale

Table 1. *Theoretical Concepts, Definitions, and Measures* (continued)

Theoretical Term	<i>Definition</i>	Conceptual Term	<i>Definition</i>	Empirical measures
Performance outcomes	<i>Performance is conceptualized to include functional and cognitive activities" (Lenz et al., 1997, p. 19). Function performance includes physical activity, ADL, and role performance or quality of life.</i>	Functional status	<i>Ability to engage in activities to care for oneself.</i>	FAC Self-care subscale Global Deterioration Scale/Functional Assessment Staging Tool MBPC ADL subscale MDS 3.0
		Quality of life	<i>Degree to which one can perform usual roles and find fulfillment in life.</i>	Alzheimer Disease Related Quality of Life Quality of Life in AD Health Survey SF-36v2

NOTE: Memory and Behavior Problem Checklist-1987R (MBPC); Neuropsychiatric Inventory (NPI); AD Assessment Scale (ADAS); Functional Abilities Checklist (FAC)

Antecedent Situational Factors. Situational antecedent factors include measures of the social and physical environments. Social environment is measured by Nursing Unit Rating Scale (NURS) and in terms of caregiver burden as measured by the Zarit Burden Interview (ZBI), the Memory and Behavior Problem Checklist-1987R (MBPC) Memory and Behavior Caregiver reaction subscale, and the Occupational Disruptiveness subscale of the Neuropsychiatric Inventory (NPI). Physical environment is measured by the Ambiance Scale (AS) and the Therapeutic Environment Screening Survey (TESS).

Nursing Unit Rating Scale (NURS). NURS measures the social environment in facilities which care for care for persons with dementia (Grant, 1994). It assesses the environment through interviews with staff describing six dimensions of the social environment including separation, stability, stimulation, complexity, control/tolerance, and continuity (Grant, 1996). These items are measured on Likert scales and with estimated percent of residents with dementia who share accommodations with cognitively intact residents (Grant, 1996). Higher scores for separation indicate less intermingling between those with and without dementia (Grant, 1996). High scores in the stability subscale indicate consistent staff caregiver assignments (Grant, 1996). High scores on the stimulation scale indicate more noise (Grant, 1996). Higher complexity scores indicate a lack of programs specifically designed for persons with dementia (Grant, 1996). Higher scores in the control/tolerance scale indicate less tolerance of behavioral symptoms that are problematic to others (Grant, 1996). Scores on the continuity scale were higher when personal information was used in developing activities and individual care plans (Grant, 1996).

Internal consistency of each subscale was acceptable to high with Cronbach α of .70-.95 (Grant, 1996). Scores between scales were weakly correlated ($r = .03-.37, p < .05$; Grant, 1996).

Discriminate validity was demonstrated with significant differences between NURS scores on dementia and non-dementia focused units for all subscales except continuity (Grant, 1996).

Zarit Burden Interview (ZBI). The ZBI measures a caregiver's feelings of burden on a personal level and in terms of role strain (Hérbert, Bravo, & Préville, 2000). It has been revised from its original version to include 22 questions like "Overall, how burdened do you feel in caring for your relative?" that are each scored between 0 (never) and 4 (nearly always; Zarit, Reever & Bach-Peterson, 1980; Zarit, Orr, & Zarit, 1985). Scores range between 0 and 88 with higher scores indicating greater burden.

The ZBI demonstrated good reliability and validity. Internal consistency is high with Cronbach α of .92 (Hérbert et al., 2000; Al-Rawashdeh, Lennie, & Chung, 2016). Its convergent validity with the Oberst Caregiving Burden Scale was good ($r = .47, .58, p < .01$; Al-Rawashdeh et al., 2016; Oberst, 1990).

Memory and Behavior Problem Checklist 1987R (MBPC). The MBPC was developed by Zarit and Zarit (1983) to measure memory deficits and challenging behaviors in individuals with AD, as well as the responses of caregivers to these deficits. It was revised to include separate subscales for ADL and Memory/Behaviors from the perspective of the person with AD as well as their caregiver's responses to the different types of behaviors (Zarit, Todd, & Zarit, 1986). The scale consists of 24 items with scores for frequency (0 never occurred to 5 occurs daily or more often) and caregiver reaction (0 no bother to 4 extremely bothersome; Zarit et al., 1986). In the sample included in this study, an additional frequency rating point was included (Schutte et al., 2003). Nine of the items correspond to ADL, while the remaining 15 items correspond to memory and behavior (Zarit, Todd, & Zarit, 1986).

The MBPC has high internal consistency (Cronbach $\alpha = .84$; Schutte et al., 2003). This scale has a documented interrater reliability of 0.80 as well as test-retest reliability of 0.80 (Gerdner, Bckwalter, & Reed, 2002; Piccininni et al., 1998). The convergent validity of the MBPC compared to other measures of cognition are low to moderate ($r = .69$ with the Mental Status Questionnaire and $.49$ with the Mini Mental State Exam), but the discrepancy may be partially attributed to the inclusion of behavioral problems measured in the MBPC which are not measured in other cognitive tests (Gerdner et al., 2002; Kahn, Goldfarb, Pollack, & Peck, 1960; Folstein, Folstein, & McHugh, 1975).

Neuropsychiatric Inventory- Nursing Home (NPI-NH). The NPI Nursing Home version was adapted from the original NPI to evaluate behavioral symptoms of AD (including delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behavior disorders, and appetite and eating disorders) for persons with AD living in nursing homes (Cummings et al., 1994; Wood et al., 2000). Modifications include rephrasing of questions to be more applicable to the nursing home setting. The NPI-NH includes an inventory of whether or not each symptom has been present in the past month, and the frequency for those that are present frequency (1 = Rarely to 4 = very often), severity (1 = mild distress to 3 = severe distress), and disruption (0 = not at all to 5 = extremely disruptive) are measured through caregiver or staff interview. The NPI-NH measures caregiver distress in response to these symptoms with its occupational disruptiveness scale (Wood et al, 1999).

Internal consistency of the NPI-NH has been measured with Cronbach α of $.67$ (Lange, Hopp, & Kang, 2004). Test-retest reliability at the 72-hour interval was good for each of the symptoms measured ($r = .55-.88$; Iverson et al., 2002). When compared with other assessments

of each item individually (for example, the CMAI for agitation and Cornell Depression scale for depression), the NPI-NH subscales had moderate convergent and discriminant validity for each individual symptoms ($r = .26-.59$; Lange et al., 2004).

Ambiance Scale (AS). The AS was developed to quantify the nature of the physical environment of long term care facilities on persons with dementia (Algase et al., 2007). The AS was adapted from a previous environmental assessment that evaluated how home-like a facility appeared (Struble, 1995). The adapted AS evaluates the environment on the basis of its likely soothing and engaging effects on persons with dementia (Algase et al., 2007). An observer uses the AS to evaluate the environment on 13 criteria and score each between -2 and +2 resulting in total scores between -26 to 26 (Algase et al., 2007). Examples of environmental criteria are stimulating or custodial and personalized or regimented (Algase et al., 2007).

The AS has good psychometric properties. Good reliability of the tool's internal consistency is demonstrated in Cronbach α of 0.89-0.91; interrater reliability was also good with no significant differences between evaluators using the same tool ($t = -0.537$, $df = 117$, $p > .05$; Algase et al., 2007). Construct validity was demonstrated with significant correlations between measures of engaging and soothing subscales ($r = .49-.62$, $p < .01$; Algase et al., 2007).

Therapeutic Environment Screening Survey (TESS). The TESS-NH was developed to assess the degree to which a facility's physical environment is equipped to meet the therapeutic needs of persons with dementia (Sloane et al., 2002). The TESS-NH was developed as a result of a NIA initiative to study special care units focused on dementia care, and was developed from previous versions (Sloan et al., 2002, Sloane & Mathew, 1990). It measures exit control, maintenance, cleanliness, safety, orientation cuing, privacy, unit autonomy, outdoor access, lighting, noise, visual/tactile stimulation, space/seating, and familiarity or home-likeness with 84

items; higher scores represent favorable attributes of the environment (Sloan et al., 2002). It is a survey rather than a scale; each domain is score individually so no absolute score range is available.

The TESS-NH has good psychometric properties. Cronbach α for each domain ranged between .33 and .83 with the lowest performance on the noise domain. Interrater reliability was high with an average agreement of 86.7%, and correlation of responses between .33 and 1.0; test-retest reliability was .88 (Sloan et al., 2002). Concurrent validity with Professional Environmental Assessment Procedure was strong ($r = .68, p < .01$; Norris-Baker et al., 1999; Sloan et al., 2002).

Antecedent Psychological Factors. Psychological antecedent factors of study include mood, psychosis, and elevated behavioral symptoms. Mood is conceptualized as the affect presentation of persons with AD, and specifically includes depression, anxiety and apathy measured by the Depression, Anxiety, and Apathy subscales of the NPI. Psychological factors of psychosis describe beliefs of sensory experiences that are not consistent with reality measured by the Delusions and Hallucinations subscales of the NPI. Other elevated behavioral symptoms are conceptualized as dysregulated actions or emotions, and are measured by the Elation, Disinhibition, Aberrant Motor Behavior, Sleep, and Irritability subscales of the NPI, the Noncognitive Behavioral subscale of the AD Assessment Scale (ADAS), and the Inappropriate behavior subscale of the Functional Abilities Checklist (FAC).

Alzheimer Disease Assessment Scale (ADAS). The ADAS was designed as a test that could detect longitudinal changes in AD patients, and measures two aspects of AD: cognitive and non-cognitive (emotional and behavioral) symptoms (Rosen, Mohs, & Davidson, 1984). The maximum possible score is 115 points, and points are deducted throughout the interview as

errors occur (Rosen et al., 1984). The cognitive subscale includes 70 of the total points, and measures memory, language, praxis, and commands (Rosen et al., 1984). The remaining 45 points measure behavior.

Internal Consistency reliability was very high (Cronbach $\alpha = .97$; Kørner, Lauritzen, & Bech, 1996). Interrater reliability was high in initial testing (.65 - .99; $p < .001$; Rosen et al., 1984). ADAS was found to have very strong concurrent validity with other measures of Alzheimer Disease symptoms (GDS, Clinical, Global Impressions, Cambridge Cognition Examination, and MMSE; $r = .89-.95$, $p < .001$; Kørner et al., 1996).

Functional Abilities Checklist (FAC). FAC was developed by the University of Iowa College of Nursing for Alzheimer's Family Role studies. The FAC consists of 28 items to measure four areas of functional ability including self-care, inappropriate behaviors, cognitive status, and agitation (Swanson, Maas, & Buchwalter, 1994). These constructs are measured with questions about activities of daily living such as dressing, eating, grooming, as well as questions about behaviors such as resisting assistance for feeding, agitation at night, threatening others (Swanson et al., 1994). Information is gathered by caregivers about behaviors from the past week, and each item is scored between 1 (never) and 4 (multiple times per day) with high scores indicating a high level of functional impairment (Swanson et al., 1994). Because two of the items have a "not applicable" response, subscales are scored by averaging the given responses resulting in scores of 1-4 for each subscale.

Internal consistency demonstrated moderate to high reliability (Cronbach $\alpha = .52-.89$; Swanson et al., 1994). Test retest reliability was good ($r = .77$; Swanson et al., 1994). Concurrent validity was demonstrated with a high correlation to the Geriatric Rating Scale which also measures functional abilities ($r = .84$; Swanson et al., 1994).

Antecedent Physiological Factors. Physical antecedent factors include comorbidities, pain, nutritional status, hearing, cognitive impairment, and fatigue. Comorbid physical conditions are measured by the Cumulative Illness Rating Scale-Geriatrics (CIRS-G). Pain is measured by the Pain Assessment in Advanced Dementia (PAIN-AD). Nutritional Status is measured by the Mini Nutritional Assessment-Short Form (MNA-SF) and NPI Appetite subscale. Hearing loss is measured by the Hearing Handicap Inventory for Elderly Screening (HHIE-S), and by hearing data in the Long Term Care Minimum Data Set (MDS 3.0). Cognitive Impairment is measured by the Mini Mental State Exam (MMSE), Severe Impairment Battery (SIB), the cognitive subscale of the ADAS, the memory behaviors frequency of the MBPC, and the cognitive status subscale of the FAC.

Cumulative Illness Rating Scale-Geriatrics (CIRS-G). The CIRS-G was developed from the original CIRS to reflect the health concerns that are important to Geriatric populations (Lin, Lin, & Gurel, 1968, Miller & Towers, 1991). The assessment is administered by a health care provider who identifies which body systems have issues and rates the severity of each issue. Scores are calculated by the total number of health systems with illnesses, the severity rating for each illness from 0 (no problem) to 4 (extremely severe), the severity index (ratio of the total score to the number of systems with problems), and the number of categories with a rating of 3 or 4 (Miller & Towers, 1991).

Interrater reliability was good; correlations were found between .78-.85 for total score and .81-.83 for number of categories for outpatients and inpatients respectively (Miller et al., 1992). Convergent validity was measured against a physician's rating of a patient's overall health on a scale of 0-50 with moderate agreement ($r = .48, p < .05$; Miller et al., 1992).

Pain Assessment in Advance Dementia (PAIN-AD). Pain-AD was developed as an observational scale to quantify severity of pain symptoms in persons with advanced dementia (Warden, Hurley, & Volicer, 2003). Categories (including breathing, vocalizations, facial expression, body language, and consolability) are scored from 0 (normal) to 2 (severe symptoms such as noisy labored breathing, hyperventilation etc.); total scores range from 0 to 10 with higher scores indicating more severe pain (Warden et al., 2003).

Internal consistency is very reliable (Cronbach $\alpha = .85$; DeWaters et al., 2008). Interrater reliability is also very high with a correlation of .98 when vignette videos were assessed (DeWaters et al., 2008). Concurrent validity was high when the PAINAD was measured against the 0-10 numeric rating scale in populations of cognitively intact and impaired patients ($r = .735, .915, p < .001$; DeWaters et al., 2008) Convergent validity was also tested by comparing PAIN-AD scores with nurse and physician ratings of pain. Pain ratings from health providers were significantly correlated with PAIN-AD scores, but with less agreement than self-reported measures ($r = .44 - .69$; Zwakhalen, 2012).

Mini Nutritional Assessment-Short Form (MNA-SF). The MNA-SF is a six-item assessment of nutritional status (Rubenstein, Harker, Salvà, Guigoz, & Vellas, 2001). The MNA-SF is an abbreviated version of the original 18-item MNA (Guigoz, Jensen, Thomas, & Vellas, 2006; Rubenstein et al., 2001). The six items include questions about intake of food, weight changes, mobility, stress or diseases, dementia or depression, and body mass index yield total scores of 0-14 points with lower scores indicating a greater risk for malnutrition (Rubenstein et al., 2001).

Reliability of the MNA-SF internal consistency was good with Cronbach $\alpha = .65$ (Guigoz, et al., 2006). Interrater reliability was good with a kappa = .78 for assessments of

institutionalized elderly (Guigoz, et al., 2006). Convergent and Divergent validity were demonstrated by MNA-SF's strong sensitivity of 97.9% and specificity of 100% to detect malnutrition compared to a clinical nutritional status assessment (Rubenstein et al., 2001).

Hearing Handicap Inventory for Elderly Screening (HHIE-S). The HHIE-S was developed as an assessment to identify hearing loss in older adults (Ventry & Weinstein, 1982). The HHIE-S includes 25 items which correspond to emotional and social/situational subscales (Ventry & Weinstein, 1982). An example of a social/situational example is "Does a hearing problem cause you to attend parties less often than you would like?" ((Ventry & Weinstein, 1982, p. 129). Each question is answered with a yes (4 points), sometimes (2 points), or never (0 points) (Ventry & Weinstein, 1982). Total scores range from 0-100, and higher scores indicate greater impairment (Ventry & Weinstein, 1982).

Cronbach α of the HHIE-S was .95, .93. and .88 for the total score and emotional and social/situational subscales respectively (Ventry & Weinstein, 1982). Using pure-tone audiometry to evaluate hearing loss in the better ear, the HHIE-S was found to have good convergent validity with a significant correlation ($r = .61$; Weinstein & Ventry 1983). The assessment was found have good to great construct validity (53-72% sensitivity, 70-84% specificity), with some variation depending on the type and degree of hearing loss used as a cut point to define hearing loss (Lichtenstien,Bess, & Logan, 1988).

Long Term Care Minimum Data Set (MDS 3.0). The MDS 3.0 is a standardized assessment of physical, clinical, psychological, psycho-social, and life care wishes of older adults who live in long term care facilities (Saliba & Buchanan, 2012). All long-term care facilities that participate in Medicare or Medicaid programs are required to maintain these data for their residents (Saliba & Buchanan, 2012). The goal of the wide collection of these data is to

report quality indicators, decide Medicare payments, and to assure appropriate care plans are developed (Morris et al., 2003). It takes just over one hour to complete on average (Saliba & Buchanan, 2012).

Development testing revealed that interrater reliability between research nurses and facility staff was good to excellent (.85-.90; Saliba & Buchanan, 2012). Validity on the basis of agreement between with diagnoses from hospital claims compared to MDS data found a positive predictive value above .7 for major diagnoses (Mor, Intrator, Unruh, & Cai, 2010). Because of the wide range of categories covered, the performance of each individual assessment must be assessed individually. The greatest threat to the reliability and validity of the MDS is known as “paper compliance,” where documentation in the form is completed to appease quality indicator standards, but does not accurately reflect the clinical reality of higher rates of delirium, depression, pain, and low oral intake (Rahman & Applebaum, 2009).

Mini Mental State Exam (MMSE). The Mini Mental State Examination (MMSE; Folstein et al., 1975) was originally developed as a brief evaluation of the cognitive state of psychiatric patients including those with affective disorders, psychoses, and dementia syndromes excluding mood and abnormal thought processes. Scores on the MMSE range from 0-30 with higher scores indicating better cognition (Folstein et al., 1975). The MMSE contains two sections. The first section assesses registration of three words, short-term memory used to recall the words, orientation to time and place, and attention to calculation through verbal responses (Folstein et al., 1975). The second section assesses language through naming objects, the ability to follow verbal and written commands, and writing. The second section also assesses visual spatial skills through the participant’s ability to copy a complex polygon shape (Folstein et al., 1975).

Reliability of internal consistency has been demonstrated in a population of hospitalized individuals (Cronbach $\alpha = 0.96$; Tombaugh & McIntyre, 1992). Interrater reliability of the MMSE was demonstrated by Folstein et al., (1975) with a high correlation of scores obtained by two examiners in hospitalized and community-dwelling individuals (.83, $p < .001$). The MMSE demonstrated test-retest reliability with no significant differences between scores obtained 24 hours apart for acute psychiatric conditions, or 28 days apart for dementia syndromes (as measured by non-significant Wilcoxon $T = 45, 42, p > 0.05$), and high correlations between first and second test scores for both groups ($r = .89, .98, p < .0001$; Folstein et al., 1975). Concurrent validity is demonstrated with the agreement between MMSE scores and the expert clinical diagnosis of cognitive difficulty (Mann-Whitney $U = 4, p < .001$; Folstein et al., 1975). The MMSE scores are similar to the Wechsler Adult Intelligence Scale (WAIS-I; Wechsler, 1955), with strong correlations demonstrated between MMSE and WAIS-I Verbal IQ and Performance IQ domains ($r = .78, .66, p < .001$; Folstein et al., 1975).

Construct validity is supported by observations that MMSE scores improve when acute cognitive conditions are treated (including acute depression, metabolically induced delirium, and head trauma; Folstein et al., 1975), and with diminished scores reflecting cognitive decline over time in longitudinal studies of persons with AD (Tombaugh & McIntyre, 1992). Construct validity of the MMSE is also supported by its high sensitivity to correctly identify those with cognitive impairment as well as its specificity to correctly identify those who are cognitively intact. The MMSE's specificity for dementia is usually moderate to high (66-100%), but MMSE may overestimate cognitive impairment in African Americans, individuals with lower than 8th grade educational attainment, and those with sensory impairment (Foreman, Fletcher, Mion, Simon, & Faculty, 1996; Leveille et al., 1998; Tombaugh & McIntyre, 1992). The differential

performance of these groups on the MMSE threatens the validity of the MMSE as a tool to identify dementia. However, the MMSE is a screening tool for cognitive impairment; it is not intended to provide a definitive diagnosis of AD and not valid for that purpose (Monroe & Carter, 2012).

Severe Impairment Battery (SIB). SIB is designed to measure cognition in those with severe cognitive limitations such as advanced AD for whom other tests of cognition are impractical or result in a floor effect (Saxton, McGonigle-Gibson, Swihart, Miller, & Boller, 1993). The SIB includes 40 items yielding scores between 0-100 with low scores indicating impairment in cognition (Saxton et al., 1993). The scale can be divided into nine subscales measuring social interaction, memory, orientation, language, attention, praxis, visuospatial ability, and construction through writing and verbal responses (Saxton et al., 1993). For an example of items used to assess memory, participants are asked to recall a sentence and the name of the examiner (Saxton et al., 1993).

Internal consistency of the SIB is very high (Cronbach $\alpha = .97$; Ahn, Kim, Ku, Saxton, & Kim, 2006). In its development testing, interrater reliability was very high with a perfect correlation of overall scores ($r = 1.0$), and good correlations between scores on each subscale ($r = .87 - 1.0, p < .001$; Saxton et al., 1993). Test-retest reliability was also high at the 14 day retest interval ($r = .85, p < .001$; Saxton et al., 1993). Concurrent validity was measured against the MMSE, and good correlations between scores on the two tools were found ($r = .74, p < .001$; Saxton et al., 1993).

Symptom: Agitation. The symptom of interest is Agitation. Agitation is the primary outcome of interest in this study. Agitation is measured by the Cohen-Mansfield Agitation

Inventor (CMAI), the agitation subscale of the FAC, and the agitation/aggression subscale of the NPI.

Cohen-Mansfield Agitation Inventory (CMAI). The CMAI was developed to quantify agitated behaviors in nursing home residents, and has also been used in community and acute-care hospital settings (Cohen-Mansfield et al., 1989; Koss et al., 1997; Kupeli et al., 2017). The CMAI a questionnaire composed of 29 agitated behaviors (Cohen-Mansfield et al., 1989). Examples of agitated behaviors include: “Pace, aimless wandering; inappropriate dress or disrobing; and screaming” (Cohen-Mansfield, 1991, p. 22). Each behavior is given a frequency score on a seven-point rating scale (1 = never, 7 = several times per hour; Cohen-Mansfield, 1991). Behaviors are reported by caregivers, and scores pertain to activities occurring over the past two weeks (Cohen-Mansfield, 1991). Later versions of the CMAI include a five-point disruptiveness scale, with a scores ranging between 1 (*never*) and five (*extremely disruptive*; Cohen-Mansfield, 1991).

Total scores range from 29 to 203; however the use of subscales for the different factors of agitation is preferred (Cohen-Mansfield 1991). Some versions of the CMAI include two additional ratings: a score of eight indicating that the behavior would have occurred if not prevented (for example, the individual would have been pacing, but could not due to being physically restrained), or a score of nine if the behavior is not applicable (such as an amputee being physically unable to kick; Cohen-Mansfield, 1991). Originally, three factors of agitated behaviors were identified including physical aggression, verbal aggression, and nonaggressive behaviors (Cohen-Mansfield et al., 1989; Finkel, Lyons & Anderson, 1992). Later studies identified four factors by separating nonaggressive behaviors into verbal and physical nonaggressive factors (Rabinowitz et al., 2005). More recently, the scale was found to be

described by only two factors categorized as aggressive and nonaggressive behaviors (Kupeli et al, 2017). Cohen-Mansfield (1991) recognizes that the factors contributing to agitated behavior differ based on population and circumstances, and suggests that researchers conduct their own factor analysis.

Criteria for identifying agitated or not agitated status involves dividing the responses into factors (such as aggressive, physically nonaggressive behavior, and verbally nonaggressive behavior) and examining the frequency of behaviors. For example, someone who demonstrated agitated and aggressive behavior with at least one aggressive behavior occurring at a frequency of several times a week, or at least two aggressive behaviors occurring at a frequency of once or twice a week, or at least three aggressive behaviors occurring at a frequency of less than once a week, or two aggressive behaviors occurring at a frequency of less than once a week but still occurring and one at a frequency of once or twice a week would be characterized as demonstrating an aggressively agitated status (Cohen-Mansfield 1991). Alternatively, Cohen-Mansfield (1991) suggests that behaviors could be weighted based on level of disruptiveness and combined accordingly. While these methods are useful for categorizing agitation versus not agitation, total scores from each factor subscale are most commonly used in analysis of research data.

The internal consistency reliability of the CMAI has generally been high. For the scale overall and aggressive, physically-nonaggressive, verbally agitated, and hiding or hoarding behaviors, Cronbach α are all .62 to .91 (Finkel et al., 1992; Rabinowitz et al., 2005). Due to the subjective nature of this rating, interrater reliability of the disruptiveness scale is indeterminate.

Concurrent validity has been demonstrated by comparing the CMAI to the Behavioral Syndromes Scale for Dementia (BSSD; Devanand et al., 1992), the Behavioral Pathology in

Alzheimer's Disease (Behave-AD; Reisberg et al., 1987), and the Ryden Aggression Scale's physically aggressive behavior subscale (RAS-PABS; Ryden, 1988). Moderate correlations were found between the CMAI and BSSD (.40-.52, $p < .05$) as well as the Behave-AD (.27-.43, $p < .05$), although correlations were nonsignificant on night shifts (Finkel et al., 1992). The CMAI had moderate agreement with the RAS-PABS (Cohen's $\kappa = .544$, $p < .001$), and the agreement increased substantially when only the physically aggressive behavior subscale of the CMAI was compared to the RAS-PABS (Cohen's $\kappa = .733$, $p < .001$; Whall et al., 2013).

In the development of the CMAI, Cohen-Mansfield and coworkers (1989) found high interrater reliability between three assessors in a population of nursing home residents. Discrepancies of one point or less was considered agreement on scores, and correlations averaged .88-.92 (Cohen-Mansfield et al., 1989). Zuidema et al., (2010) reported interrater reliabilities of .61 to .73 on the three agitation subscales in a population of Dutch nursing home residents. Conversely, Finkel and others (1992) found lower interrater reliability of only .41, with the lowest agreement of only .26 on the physically nonaggressive behaviors subscale in a population of institutionalized elderly adults. In the community, interrater reliability (as measured by discrepancies of zero or one point) was high at .92 (Koss et al., 1997).

Performance outcome: Functional status and quality of life. Functional Status and quality of life are secondary outcome variables. Functional Status is conceptualized as the ability to engage in activities to care for oneself, and is measured by the self-care subscale of the FAC, Global Deterioration Scale (GDS), Functional Assessment Staging Tool (FAST), MBPC ADL subscale, and information about functional abilities status from the MDS 3.0. Quality of Life conceptualized as the degree to which one can perform usual roles and find fulfillment in

life. Quality of life is measured by the Quality of Life in AD (QOL-AD), AD Related Quality of Life (ADRQL), and the Health Survey 36 Short Form (SF-36).

Global Deterioration Scale (GDS). GDS is used to evaluate the stage of severity in AD symptoms from 1 (no cognitive decline) to 7 (very severe cognitive decline) through a 50-point assessment measuring memory, executive function, and social function (Reisburg, Ferris, de Leon, & Crook, 1982). Each stage is described with associated clinical characteristics including functional status, behavioral and psychiatric problems (Reisberg et al., 1982). It was designed to help caregivers or families understand the disease course of AD, and set realistic expectations for the performance abilities and care needs of individuals with AD (Reisberg et al., 1982).

The authors state that they developed the GDS with a conceptual approach rather than through psychometric and statistical methods; therefore internal consistency was not measured (Eisdorfer et al., 1992). Good interrater reliability has been found using the GDS ($r = .82$; Foster, Sclan, Welkowitz, Boksay, & Seeland; 1988). Convergent validity was found between GDS stage and PET scans of brain regions affected by AD lesions which utilize less glucose ($r = .69-.83, p < .05$; Ferris et al., 1980).

Functional Assessment Staging (FAST). The FAST is a functional assessment questionnaire for individuals with AD. It was developed by Reisberg (1986) through an expansion of the functional components of the GDS to describe progressive functional changes in AD. Like the GDS, the FAST corresponds to the seven stages of AD with decreased functional ability at higher levels (Reisberg, 1986). The FAST further divides the late stages of AD with eleven sub-stages describing the functional considerations of GDS stage 6 and 7 in greater detail (for a total of 16 FAST levels; Reisberg, 1986).

Interrater reliability for the FAST was high (ICC 0.87, $p < .01$; Sclan & Reisberg, 1992). Concurrent validity between the FAST and ten other psychometric measures of AD were highly correlated ($r = .59-.73$; $p < .01$, Reisberg et al., 1984). Concurrent validity with the Ordinal Scales of Psychological Development (used as a measure of AD severity stage) was correlated with FAST ($r = -.79$, $p < .01$; Sclan & Reisberg, 1992).

Quality of Life in AD (QOL-AD). QOL-AD was designed as a tool to measure quality of life specifically in persons with dementia (Logsdon, Gibbons, McCurry, & Teri, 1999). It contains 13 questions covering physical health, mood, memory, social relationships, participation in meaningful activities, financial situation, overall assessment of self, and quality of life (Logsdon et al., 1999). Each item is rated by the individual on a four-point Likert scale from 1 (poor) to 4 (excellent; Logsdon et al., 1999). Total scores range from 13 to 52 with higher scores indicating a higher quality of life (Logsdon et al., 1999). This assessment includes one version for participants to self-report their QOL, and another version for caregivers to report each question as a proxy for the participant. Composite scores are calculated by doubling the self-reported score, adding in the proxy reported score, and then dividing by three (Logsdon et al., 1999).

The QOL-AD has good internal consistency Cronbach α for self-reported, proxy-reported, and composite scales (.88, .87, .90, Geschke et al., 2013; Logsdon et al., 1999). Test-retest reliability was acceptable for both patients and caregiver reports (ICC = .76, .92; Logsdon et al., 1999). Divergent validity was noted with lower correlations to MMSE scores ($r = .12, .02$, $p > .05$ for patient and caregiver responses), and convergent validity was noted with significant correlations to other measures of each domain such as reports of engagement in activities, psychological status, and physical functions with higher correlations between caregiver reports

of these items (Logsdon, Gibbons, McCurry, & Teri, 2002). Generally, self-rated scores are higher than proxies, but this phenomenon is addressed by the increased weighting of the self-rated score in the calculation of composite score (Geschke et al., 2013; Huang et al., 2009; Logsdon et al., 2002; Logsdon et al., 1999).

AD Related Quality of Life (ADRQL). ADRQL is another measure of Quality of Life for individuals with AD. It was developed through focus groups with caregivers of individuals with AD and expert panels (Rabins, Kasper, Kleinman, Black, & Patrick, 1999). It measures five domains (social interaction, awareness of self, feelings/mood, enjoyment of activities, and response to surroundings) through observations of actions and assessments of subjective states. Scores are calculated with quality of life indicators weighted by the importance of each domain (as ranked by caregiver input during tool development). Responses are recorded from the caregiver of the person with AD as a proxy in a structured interview format. Questions pertain to behaviors observed in the past 2 weeks; respondents are asked to agree or disagree if a statement describes the person with AD (for example “He/She smiles or laughs when around other people;” Rabins et al., 1999, p. 42). The total score is obtained by determining the percent of affirmative points scored in each domain; higher scores indicate a higher quality of life.

Cronbach α was .86 for the total scale; subscales ranged from .56 to .86 indicating acceptable to good reliability of internal consistency (Kasper, Black, Shore, & Rabins, 2009). Content validity is supported by the development of the scale through qualitative methods of data collection from patients, experts, and the literature (Rabins et al., 1999).

Health Survey 36 short form (SF-36). The SF-36 questionnaire measures health-related quality of life (Ware & Sherbourne, 1992). It was designed to measure health status in the large Medical Outcomes Study (Ware & Sherbourne, 1992). It can be divided into subscales

describing physical function, role limitations related to health problems, pain, social function, emotional well-being, role limitations related to emotional problems, energy/fatigue, and perceived general health (Ware & Sherbourne, 1992). Scores from each domain are transformed to a range of 0 (poor health) to 100 (excellent health; McHorney, Ware, & Raczek, 1993).

Internal consistency has been demonstrated with high Cronbach α (.81-.88; Steward, Hays, & Ware, 1988). Convergent and discriminant validity tested well against comorbid disease burden and other measures of these factors (McHorney et al., 1993). In persons with dementia, Cronbach α was good for most subscales (.64-.92 on each subscale), but slightly lower for individuals whose MMSE scores were below 16 (.51-.90; Geschke, Fellgiebel, Laux, Schermuly, & Scheurich, 2013). Concurrent validity with the QOL-AD has been demonstrated with significant correlations between self-rated scores and QOL-AD composite scores ($r = .29-.62; p < .05$; Geschke et al., 2013).

Other Participant Information: In addition to the formal instruments, further individual information was collected including: demographic data (age, sex, racial/ethnic background, level of education, and type of career); age at time of AD diagnosis; years since initial diagnosis; type of residence (community or institutional dwelling).

Data Analysis

Data Management

Original data were stored in an electronic database. Data were managed and analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.0. Path analyses were calculated with the Analysis of a Moment Structures (AMOS) graphics module of SPSS. First, data were converted into SPSS format. Next, individual data files from specific instruments and studies were matched by participant identification numbers and added to a new SPSS file.

Duplicate observations and time points were removed, as well as variables that were not pertinent to the current study.

Missing Data

Missing data is present in most large datasets (Kline, 2011). This study is no exception. As this secondary analysis pulled data from multiple sources of data, there were frequent occurrences of missing data. Not all studies used the same instruments to measure data, and there were also isolated cases of item-level missing data. Missing data assessed for pattern and frequency. Variables measured in only a single study with fewer than 20 responses were removed. Remaining variables were tested for significant differences between participants with missing data and those with measured data. Little's Test for Missing Completely at Random found significant patterns of missing data, indicating that imputation techniques are inappropriate for this sample ($\chi^2 = 167.9, p < .001$; Little, 1988). Missing Value Analysis in SPSS was then used to identify the maximum subset of data with complete responses for main analyses. Other variables were analyzed individually with missing cases removed list wise as secondary outcomes.

Sample Summary Analysis

All variables were individually summarized through descriptive statistics. Central tendency (measured with mean, median, and/or mode) and dispersion (measured by standard deviation, range and/or interpercentile measures) were calculated to define the data within the sample.

Data Analysis for each Specific Aim

Aim 1: Describe the phenomenon of agitated behavioral symptoms in persons with AD within the Theory of Unpleasant Symptoms.

Hypothesis: The Theory of Unpleasant Symptoms will adequately describe the antecedents and consequences of agitated behavioral symptoms in persons with AD.

Aim 1 is evaluated by the degree to which the final path analysis model represents all theoretical constructs predicted in the TOUS. First, an exploratory factor analysis is used to reduce the empirical measures into factors that represent each of the theoretical concepts suggested by the TOUS (Munro, 2005). A large number of variables are present in the existing data set (8 demographic measures and 40 instruments). One of the greatest conceptual strengths held by the TOUS is its extremely broad scope in considering all possible antecedents and consequences relevant to an individual's experience of symptoms (Lee, Vincent, and Finnegan, 2017). From the pragmatic perspective of theory testing however, it is not feasible to include variables that fully capture each possible dimension of the concepts described in the TOUS into a single testable model. To reconcile this challenge, the data were reduced and summarized through an exploratory factor analysis.

Next, the relationships between theoretical constructs were tested with path analysis. Variables that describe each of the three main concepts within the TOUS (antecedents, symptoms, and performance outcomes) are analyzed through exploratory factor analysis. The resultant factors then take the place of measured data within the path model as proxy variables for the indicators which they represent. The path analysis is used to test the main relationships in TOUS and determine the degree to which the composition of model matches the variables described in TOUS.

Path analysis calculates regressions between each factor, and examines direct effects of independent (exogenous) variables on dependent (endogenous) variables as well as indirect mediator effects of independent variables (Munro, 2005). Path analyses provide evidence about whether or not the hypothesized model fits the observed data (Munro, 2005). The hypothesized model substructured from the TOUS is shown in figure 3.

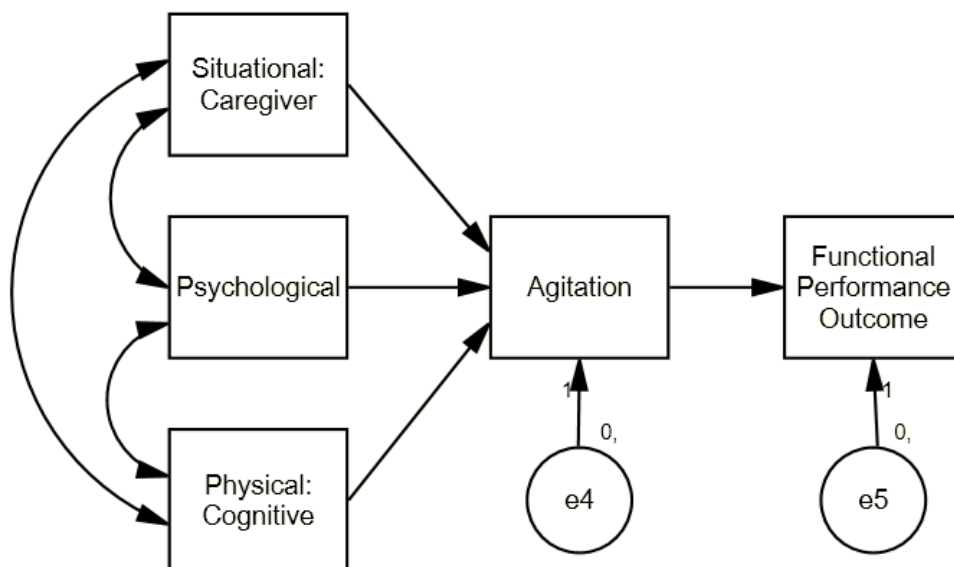


Figure 3. Proposed path model of predictors and outcomes of agitation.

Aim 2: Determine the effect of situational (physical and social environment), psychological (anxiety and depression), and physiological factors (comorbidities, pain, nutritional status, hearing, cognitive impairment, and fatigue) on agitation in persons with AD.

Hypothesis:

- (1) Supportive and stimulating physical and social environments will have a negative direct effect on agitation.
- (2) Comorbid psychological states will have a positive direct effect on agitation.

- (3) Comorbid physical conditions, pain, inadequate nutritional status, hearing loss, cognitive impairment, and fatigue will have a direct positive effect on agitation.

Aim 2 was tested with the examining the regression coefficients in the path analysis model best fitting the data. The magnitude, direction, and significance of the path coefficients from situational, psychological, and physical factors to agitation were evaluated. Bivariate relationships (Pearson's correlation) between individual measures and the agitation outcome were also used to test these hypotheses.

Aim 3: Determine the effect of situational, psychological, physical antecedent factors and agitation on performance outcomes (functional status and quality of life) in persons with AD.

Hypothesis:

- (1) Supportive and stimulating physical and social environments will have an indirect positive effect on functional status and quality of life through reduced agitation.
- (2) Comorbid psychological states will have an indirect negative effect on functional status and quality of life through increased agitation.
- (3) Comorbid physical conditions, pain, nutritional status, hearing loss, cognitive impairment, and fatigue will have an indirect negative effect on functional status through increased agitation.
- (4) Agitation will have a negative direct effect on functional status and quality of life.

Aim 3 was tested by examining the regression coefficients in the path analysis model best fitting the data. The magnitude, direction, and significance of the path coefficients from situational, psychological, and physical factors to functional ability were evaluated. The paths from agitation to functional ability were also examined. Bivariate relationships (Pearson's

correlations) between individual measures and the functional performance outcome are also used to test these hypotheses.

CHAPTER 4: RESULTS

The results chapter is divided into five sections. This chapter begins with a description of the study sample. In this descriptive statistics section, demographic data and descriptive information for all study instruments is summarized. In the second section, preliminary analyses of correlations between instruments measuring each study variable are presented. The final three sections report results of analyses for each of the three specific aims. The first aim is evaluated by first performing an exploratory factor analysis. Next the path analysis results relating the factors are presented. The second aim is tested by evaluating relationships between the independent variables and outcome of agitation with an examination of path coefficients. The third aim is tested by evaluating relationships between the independent variables and the performance outcomes. The final 2 sections concerning aims 2 and 3 conclude with results of bivariate Pearson's correlation analyses to explore relationships between key variables that were not captured in the path analysis.

Description of Sample and Key Variables

Study Sample Characteristics

Data from a sample of 110 individuals with AD were analyzed in this study. A summary of demographic data is presented in Table 2. Most participants were female (72.9%, $n = 72$). Nearly all of the participants identified as white (96.3%, $n = 103$). Participants had most commonly had attained a high school diploma (27.2%, $n = 22$), with more reporting higher educational attainment than lower (45.7%, $n = 37$ above high school diploma). Participants most commonly reported blue-collar work experience (22.4%, $n = 19$). Ages of participants ranged from 59 to 101 years with a mean of 83.3 years ($SD = 8.3$). The time since AD diagnosis ranged from 0 to 23.7 years with a mean of 9.2 years ($SD = 5.2$).

Table 2. *Demographic Characteristics of the Sample*

Sample Demographics	<i>n</i>	Percentage
Gender	107	
Male	29	27.1
Female	78	72.9
Ethnicity	107	
White	103	96.3
African American	1	0.9
Hispanic	1	0.9
Native American	1	0.9
Other	1	0.9
Level of Education	81	
Attended grade school	2	2.5
Completed 8 th grade	13	16.0
Attended high school	7	8.6
High school diploma	22	27.2
Attended college	16	19.8
Associate degree	9	11.2
Bachelor's degree	6	7.4
Postgraduate courses	2	2.5
Master's degree	3	3.7
Ph.D.	1	1.2
Occupation	85	
Professional	12	14.1
White-collar	13	15.3
Blue-collar	19	22.4
Farmer	6	7.1
Homemaker	17	20.0
Other	17	20.0
None	1	1.2
Residence	110	
Community dwelling	27	24.5
Institutional care residence	83	75.5
Sample Continuous Demographics	Mean ± <i>SD</i>	Range
Age in years	83.3 ± 8.3	59.0 – 101.6
Years since AD diagnosis	9.2 ± 5.2	0 – 23.7

Descriptive Results for Key Variables

All instruments used to collect data were examined for central tendency and dispersion of scores with means, standard deviation, and range of reported scores. The possible range of scores is also reported. The sample size of each instrument is also reported. Results are summarized in Table 3. Data for some measures were not available (Nursing Unit Rating Scale, Ambiance Scale, Therapeutic Environment Screening Survey, and Long Term Care Minimum Data Set 3.0). Results are discussed by study variable below.

Instruments measuring situation. Four instruments measured data about situation related to caregiver reactions. All scales were scored with higher scores indicating more caregiver burden. The ZBI had only five respondents, the two MBPC subscales had 28 respondents each, and the NPI Occupational disruption scale had 48 responses. All scales indicated low to moderate levels of caregiver burden with maximum scores of less than 61% of possible points. Mean scores all fell between 10% (MBPC ADL Caregiver Reaction subscale) and 28% (MBPC Memory and Behavioral Caregiver Reaction subscale) of the maximum possible points.

Table 3. Descriptive Results by Instrument

Instrument	<i>n</i>	Possible Range	Observed Range	Mean	Standard Deviation
Situational Antecedents					
Zarit Burden Interview score	5	0-88	5-38	18.20	12.19
MBPC Memory and behavior caregiver subscale	28	0-96	4-58	26.54	14.63
MBPC ADL Caregiver reaction subscale	28	0-36	0-12	3.64	3.63
NPI Occupational disruptiveness subscale	48	0-60	0-24	6.42	6.54
Psychological Antecedents					
NPI Depression subscale	48	0-12	0-8	0.94	1.83
NPI Anxiety subscale	48	0-12	0-12	0.73	2.56
NPI Apathy subscale	48	0-12	0-12	5.35	4.97
NPI Delusions subscale	48	0-12	0-12	1.08	2.60
NPI Hallucinations subscale	48	0-12	0-12	0.56	1.99
NPI Elation subscale	48	0-12	0-4	0.23	0.91
NPI Disinhibition subscale	48	0-12	0-9	0.58	1.90
NPI Motor subscale	48	0-12	0-12	2.21	3.97
NPI Sleep subscale	48	0-12	0-12	0.40	1.85
NPI Irritability subscale	48	0-12	0-12	3.10	3.78
ADAS Non-cognitive behavioral subscale	52	0-45	0-28	6.31	5.52
FAC Inappropriate behavior subscale	81	1-4	1-4	2.92	0.90
Physical Antecedents					
Cumulative Illness Rating Scale-Geriatrics	18	0-56	3-31	18.56	6.91
Pain Assessment in Advanced Dementia	18	0-10	0-7	0.89	1.64
Mini Nutritional Assessment	18	0-14	4-13	7.78	2.46
NPI Appetite subscale	48	0-12	0-12	1.94	4.10
HHIE-S	5	0-100	6-22	13.60	5.90
Mini Mental State Exam	5	0-30	14-30	22.80	6.30
Severe Impairment Battery	72	0-100	0-100	51.45	36.68
ADAS Cognitive subscale	15	0-70	10-48	33.27	13.23
MBPC Memory Behaviors Subscale	31	0-120	19-111	56.03	25.15
FAC Cognitive Status subscale	82	1-4	1.00-3.80	1.75	0.83

Table 3. Descriptive Results by

Instrument (Continued)

Instrument	<i>n</i>	Possible Range	Observed Range	Mean	Standard Deviation
Agitation					
Cohen-Mansfield Agitation Inventory	66	29-203	29-86	43.27	12.65
FAC Agitation subscale	83	1-4	1.00-4.00	1.88	0.77
NPI Agitation subscale	48	0-12	0-12	3.56	4.18
Functional Performance					
FAC Self-care subscale	83	1-4	1.13-4.00	3.01	0.64
GDS/FAST	91	1-11	3-9	5.56	1.27
MBPC ADL subscale	31	0-45	0-21	8.65	5.93
ADRQL	5	0-100	83.6-100	95.36	6.84
QOL-AD	5	13-52	36-43	39.40	2.61
SF-36	5	0-100	84-100	92.60	6.12

NOTE: Memory and Behavior Problem Checklist-1987 (MBPC); Neuropsychiatric Inventory (NPI); Activities of Daily Living (ADL); Alzheimer Disease (AD); Alzheimer Disease Assessment Scale (ADAS); Functional Abilities Checklist (FAC), Hearing Handicap Inventory for Elderly Screening (HHIE-S); Global Deterioration Scale (GDS); Functional Assessment Staging Tool (FAST); Alzheimer Disease Related Quality of Life (ADRQL); Quality of Life in Alzheimer Disease (QOL-AD); Health Survey 36 Short Form (SF-36)

Instruments measuring psychological states. Twelve scales measured psychological states and behaviors. All scales were scored with higher scores indicating more symptoms or behavioral difficulties. Ten subscales of the NPI (depression, anxiety, apathy, delusions hallucinations, elation, disinhibition, aberrant motor behaviors, sleep, and irritability) each had 48 responses. The ADAS non-cognitive behavioral subscale included responses from 52 individuals, and the FAC inappropriate behavior subscale included responses from 81 individuals.

Overall, a variety of responses were observed on most of the subscales, with the exception of the elation, depression, and disinhibition subscales with highest recorded responses of only 4, 8, and 9 out of 12 possible points. Apathy was the NPI subscale with the highest average score ($M = 5.35$, $SD = 4.97$), whereas elation was reported the least ($M = 0.23$, $SD = 0.91$). ADAS non-cognitive behavioral subscale responses fell to the lower end of the possible range, with a maximum reported score of 28 out of 45 possible points, and a mean score of 6.31 ($SD = 5.52$). FAC inappropriate behavior scores represented the entire possible range of responses, with a mean score of 2.92 out of 4 ($SD = 0.90$).

Instruments measuring physical comorbidities. Ten instruments measured several dimensions of physical factors including: CIRS-G quantifying comorbid disease burden; Pain in AD; nutrition and eating behaviors measured by the MNA and NPI appetite subscale; Hearing measured by the HHIE-S; Cognition measured by the MMSE, SIB, ADAS Cognitive subscale, MBPC memory-behaviors subscale, and FAC cognitive status subscale. Scales were interpreted with higher scores indicating greater impairment, except for the MNA, MMSE, and SIB in which lower scores indicated more impairment.

The largest samples were obtained with the FAC cognitive subscale and SIB ($n = 82$ and 72 respectively). The NPI appetite and MBPC memory behaviors subscales had samples of 48 and 31 participants respectively. Samples of 15 to 18 responses were returned in the CIRS-G, Pain in AD, MNA, and ADAS Cognitive Subscale. Small samples ($n = 5$) were returned for the HHIE-S and MMSE. Most samples included scores representing the full spectrum of possible responses. The least variety of responses was observed with the HHIE-S (observed scores ranged from $6-22$; possible scores ranged from $0-100$), the CIRS-G (observed scores ranged from $3-31$; possible scores ranged from $0-56$) and the MMSE (observed scores ranged from $14-30$; possible scores ranged from $0-30$). All of the scores with limited ranges of reported scores also had few responses.

The greatest levels of impairment were compared across scales with the percent of possible points (or inverse in the case of MNA, MMSE, and SIB). Overall, participants had moderate levels of cognitive impairment on average as measured by the SIB and ADAS cognitive subscales. The highest average levels of impairment were recorded by the SIB ($M = 51.45$, $SD = 36.68$; lower scores indicate greater impairment), ADAS cognitive subscale ($M = 33.27$, $SD = 13.23$), MBPC memory behaviors subscale ($M = 56.03$, $SD = 25.15$), and the MNA ($M = 7.78$, $SD = 2.46$; lower scores indicate greater risk for malnutrition). The lowest average level of impairment was measured by the Pain-AD with mean response of 0.89 ($SD = 1.64$).

Instruments measuring agitation. The three instruments measuring agitation were the CMAI, FAC agitation subscale, and NPI agitation subscale. Sample sizes were 66 , 83 , and 48 respectively. All three instruments were scored with higher values indicating more agitated behavioral symptoms. The NPI agitation and FAC agitation scales returned responses from the entire range of possible scores; the CMAI returned a maximum of only 86 out of 203 possible

points. On average, the scales indicated low to moderate levels of agitation. The CMAI had the lowest mean score compared to total possible points ($M = 43.27$; $SD = 12.65$) and the FAC agitation subscale had the highest mean score compared to total possible points ($M = 1.88$, $SD = 0.77$).

Instruments measuring functional performance. Seven instruments measured the functional ability and quality of life dimensions of functional performance. Functional ability was measured by the FAC self-care subscale, GDS/FAST, and the MBPC ADL subscale. Higher scores indicated greater functional impairment. Measures of functional ability had 91, 83, and 31 responses for the GDS/FAST, FAC self-care, and MBPC ADL subscales. Quality of life was measured by the ADRQL, QOLAD, and HS-36. High scores indicated higher quality of life. Quality of life measures each had 5 responses.

The measures of functional ability had good representation of the full range of possible scores. The mean scores of the FAC self-care subscale and GDS/FAST were high ($M = 3.01$, $SD = 0.64$, 1.27), indicating a high degree of difficulty with functional ability. The mean score of the MBPC ADL subscale was lower ($M = 8.65$, $SD = 5.9$), indicating less difficulty with functional ability measured by this instrument and within this community-dwelling subset of the sample. The measures of quality of life all measured relatively high quality of life, with a highest percent of possible points obtained on the ADRQL ($M = 95.36$, $SD = 6.84$).

Preliminary Statistical Analysis

Correlations Between Measures of Concepts

Situational factors. Correlations between measures of situation were calculated. For the concept of situational factors, correlations between caregiver measures were only available for the two subscales of the MBPC because different tools were used in each different parent study

sample. Moderate Pearson's correlations were found between the MBPC memory behavior and MBPC ADL caregiver reaction subscales ($r = .59, p < .001$).

Psychological states. Correlations between measures of psychological states and behaviors are presented in Table 4. Low correlations were found between depression and anxiety ($r = .31, p = .034$), delusions ($r = .36, p = .012$), and disinhibition ($r = .35, p = .014$), with a low inverse correlation to the FAC inappropriate behavior ($r = -.39, p = .007$). Low to moderate correlations were also found between anxiety and delusions ($r = .49, p < .001$), disinhibition ($r = .45, p = .001$), aberrant motor behavior ($r = .39, p = .006$), and irritability ($r = .35, p = .016$). A low inverse correlation was found between apathy and disinhibition ($r = -.34, p = .019$). Delusions were moderately correlated with hallucinations ($r = .51, p < .001$), disinhibition ($r = .47, p = .001$), aberrant motor behavior ($r = .42, p = .003$), and irritability ($r = .38, p = .007$). Low correlations were observed between hallucinations and aberrant motor behavior ($r = .45, p = .001$) and irritability ($r = .37, p = .009$). Elation was correlated with no other psychological instruments. Disinhibition was moderately correlated with aberrant motor behavior ($r = .47, p = .001$), and ADAS non cognitive behavior ($r = .51, p = .004$). Aberrant motor behavior was weakly correlated with irritability ($r = .39, p = .007$). Sleep disturbances were not significantly correlated with other factors.

Physical factors. Correlations between physical factors are presented in Table 5. A very strong inverse correlation was seen between the CIRS-G and MMSE scores ($r = -.96, p = .011$). A moderately strong correlation was seen between MNA and SIB ($r = .62, p < .006$). SIB scores had a low inverse correlation with FAC cognition scores ($r = -.30, p = .015$). The ADAS cognitive scale was strongly correlated with the FAC cognition scores ($r = .88, p < .001$). The MBPC memory scale was moderately correlated with FAC cognition scores ($r = .65, p = .030$).

The NPI appetite subscale, HHEI-S, and Pain Scores were not correlated with other measures. Comparisons were not possible between ADAS cognitive subscale, MBPC memory behaviors subscale, and HHIE-S and other scales because of small sample sizes of these tools.

Agitation. Correlations between measures of agitation are presented in Table 6. Significant low correlations were found between the CMAI and FAC agitation subscale ($r = .39$, $p = .002$). Correlations between CMAI and NPI agitation subscale or FAC and NPI agitation subscales were not significant.

Performance outcomes. Correlations between measures of quality of life and functional ability performance outcomes are presented in Table 7. Significant low correlations were found between the FAC self-care and GDS/FAST scores ($r = .43$, $p < .001$). Scores for GDS/FAST had low correlations with MBPC ADL ($r = .40$, $p = .025$), and strong inverse correlations to ADRQL ($r = -.96$, $p = .010$). Scores of instruments measuring quality of life were not correlated with each other, although sample sizes were small. Correlations between measures of quality of life and the FAC self-care subscale or MBPC ADL subscale could not be calculated because these tools were not used in the same studies.

Table 4. *Pearson Correlations: Psychological Measures*

Results: <i>r</i>	NPI Depress	NPI Anxiety	NPI Apathy	NPI Delusion	NPI HLNs	NPI Elation	NPI Dis- inhibit	NPI Motor	NPI Sleep	NPI Irritabilit	ADAS non cog
FAC Inapp. behav.	-.385**	0.006	0.196	-0.037	0.047	0.036	-0.039	0.194	0.112	0.14	-0.005
ADAS Non cog	0.215	-0.182	-0.224	0.094	-0.05	0.085	.509**	0.165	-0.17	0.058	1
NPI Irritability	0.161	.346*	0.096	.382**	.374**	0.049	0.169	.387**	.361*	1	
NPI Sleep	0.114	0.207	0.172	0.068	-0.06	-0.055	0.096	0.075	1		
NPI Motor	0.228	.391**	0.1	.423**	.449**	-0.091	.469**	1			
NPI Dis-inhibit	.354*	.454**	-.338*	.472**	-0.02	-0.079	1				
NPI Elation	0.189	-0.074	-0.089	-0.108	-0.07	1					
NPI HLNs	0.098	-0.082	-0.001	.505**	1						
NPI Delusion	.360*	.493**	-0.221	1							
NPI Apathy	-0.274	-0.022	1								
NPI Anxiety	.306*	1									
NPI Depress	1										

NOTE: Neuropsychiatric Inventory (NPI); Depression (Depress); Hallucinations (HLNs); Alzheimer Disease Assessment Scale (ADAS); Non-cognitive (non cog); Functional Abilities Checklist (FAC), Inappropriate Behavior (inapp. behav.)

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Table 5. Pearson Correlations: Physiological Measures.

Results: <i>r</i>	CIRS-G	PainAD	MNA	NPI Appetite	HHIE-S	MMSE	SIB	ADAS Cognitive	MBPC Memory Behavior	FAC Cognitive Status
CIRS-G	1	.006	-.338	.171	-.218	-.955*	-.443	.a	.a	-.047
PainAD		1	.052	-.157	-.062	.406	-.029	.a	.a	.056
MNA			1	-.505	-.423	-.295	.624**	.a	.a	-.233
NPI Appetite				1	.a	.a	.029	.a	.a	-.075
HHIE-S					1	.387	.130	.a	.a	.a
MMSE						1	.783	.a	.a	.a
SIB							1	.a	.a	-.298*
ADAS Cognitive								1	.397	.882**
MBPC Memory Behaviors									1	.651*

NOTE: Cumulative Illness Rating Scale–Geriatrics (CIRS-G); Mini Nutritional Assessment (MNA); Severe Impairment Battery (SIB); Memory and Behavior Problem Checklist-1987 (MBPC); Alzheimer Disease (AD); Alzheimer Disease Assessment Scale (ADAS); Functional Abilities Checklist (FAC), Hearing Handicap Inventory for Elderly Screening (HHIE-S).

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

.a = No comparative sample was available.

Table 6. Pearson Correlations: Agitation Measures.

Results: <i>r</i>	Cohen-Mansfield Agitation Inventory	FAC Agitation subscale	NPI Agitation subscale
Cohen-Mansfield Agitation Inventory	1	.389**	.229
FAC Agitation subscale		1	.211
NPI Agitation subscale			1

NOTE: Functional Abilities Checklist (FAC); Neuropsychiatric Inventory (NPI).

** Correlation is significant at the 0.01 level (2-tailed).

Table 7. Pearson Correlations: Performance Outcome Measures.

Results: <i>r</i>	FAC Self-care	GDS/FAST	MBPC ADL	ADRQOL	QOL-AD	SF-36v2
FAC Self-care	1	.425**	.186	.a	.a	.a
GDS/FAST		1	.402*	-.959*	-.160	-.224
MBPC ADL			1	.a	.a	.a
ADRQOL				1	.075	.324
QOLAD					1	-.674

NOTE: Functional Abilities Checklist (FAC); Global Deterioration Scale (GDS); Functional Assessment Staging Tool (FAST); Memory and Behavior Problem Checklist-1987 (MBPC); Activities of Daily Living (ADL); AD related quality of life (ADRQL); Quality of life in AD (QOL-AD); Health Survey Short Form (SF-36)

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

.a = Cannot be calculated because no comparative sample was available.

Aim 1: Results of Statistical Analysis

Aim 1: Describe the phenomenon of agitated behavioral symptoms in persons with AD within the Theory of Unpleasant Symptoms.

Hypothesis: The Theory of Unpleasant Symptoms will adequately describe the antecedents and consequences of agitated behavioral symptoms in persons with AD as determined by the best-fitting path analysis.

The first aim sought to describe the phenomenon of agitated behavioral symptoms in person with AD within the Theory of Unpleasant Symptoms (TOUS) by constructing a path model based on the theory, and then determining if the model that best fits the data contains all important concepts described in the theory. To test the hypothesis that the TOUS adequately describes all aspects of agitated behavioral symptoms, instruments that best describe the theoretical concepts were first identified through exploratory factor analysis. Then, a path analysis of these factors was calculated to identify the model that best fits the data.

Exploratory Factor Analysis

Antecedent Factors. The TOUS indicates that predictors of symptoms fall into three categories: situational, psychological, and physiological predictors. Exploratory Factor Analysis was used to determine which of the instruments measured related concepts. The Missing Values Analysis identified the instruments which had been used most consistently to provide a complete sample of 48 participants. The NPI subscales, FAC subscales, and SIB were included in the analysis. Because the SIB instrument is scored with higher values indicating less impairment, scores were recoded to inverse scoring to match the scoring scheme for other instruments and aid in ease of comparison. MBPC subscales, ADAS subscales, ZBI, CIRS-G, Pain Assessment in AD, MNA, HHEI-S, and MMSE were not included in this analysis.

The remaining data were suitable for Exploratory Factor. The sample of 48 participants measured across all 15 instruments is sufficient for the minimum of two observations per variable, and approaching the preferred ratio of 5-6 observations per variable after further variables were removed from the analysis pool later in the process (Kim & Mueller, 1978; Tabachnick & Fidell, 2013). As demonstrated in the correlation matrix previously presented in Tables 4 and 5, numerous variables had correlations above .30 to further support the use of exploratory factor analysis for these data. The Kaiser-Meyer-Olkin Measure of Sampling Adequacy was above the recommended value of .50 at .632 (Kaiser, 1974). Finally, statistical significance found in Bartlett's Test of Sphericity indicates that the correlation matrix provided by the data is appropriate for factor analysis (Munro, 2005; $\chi^2 = 240.6, p < .001$).

The first iteration of the factor analysis revealed that the NPI elation measure did not load strongly on any factors. This matches findings from the correlation Table 4, and NPI elation was removed from further analysis. On the next analysis, NPI sleep and apathy subscales were not loaded strongly on any factors with eigenvalues above 1, and these were also eliminated from further analysis.

Principal components method of extraction was used to identify factors from SIB scores, FAC inappropriate behavior and cognitive status subscales, and NPI occupational disruption, depression, anxiety, delusions, hallucinations, disinhibition, aberrant motor behavior, and irritability subscales. The percentage of the variance in each variable which is explained by all extracted factors, or extracted communalities of each factor, is illustrated in Table 8.

The Scree Plot was examine to determine the number of factors that best describe the data (see figure 4). The scree plot illustrates a marked change in slope after component number 3. This "elbow" point in the graph illustrates that three factors should be extracted, as further

factors explain less and less additional variance. The three factor solution is further supported by the criteria of extracting only factors with eigenvalues greater than 1, as well as matching the three factors suggested by the TOUS.

Table 8. *Communalities between predictor variables*

Instrument	Initial	Extraction
NPI Occupational disruptiveness	1.000	0.809
NPI Depression subscale	1.000	0.564
NPI Anxiety subscale	1.000	0.695
NPI Delusions subscale	1.000	0.646
NPI Hallucinations subscale	1.000	0.885
NPI Disinhibition subscale	1.000	0.670
FAC Inappropriate behavior	1.000	0.795
FAC Cognitive Status subscale	1.000	0.432
SIB (Inverse)	1.000	0.671
NPI Aberrant Motor Behavior	1.000	0.549
NPI Irritability subscale	1.000	0.539

NOTE: Neuropsychiatric Inventory (NPI), Functional Abilities Checklist (FAC), Severe Impairment Battery (SIB).

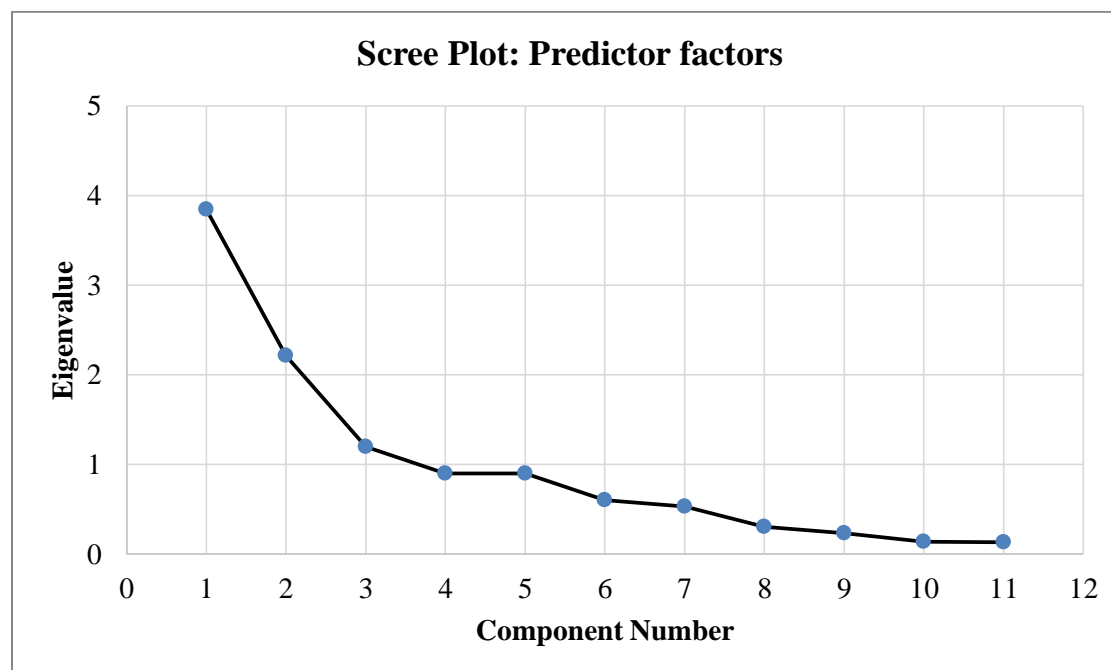


Figure 4. Scree Plot of predictor factors

Table 9. Total Variance Explained: Predictor Variables

Component	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
	Total	Variance % of	Cumulative %	Total	Variance % of	Cumulative %	Total	Variance % of	Cumulative %
1	3.844	34.946	34.946	3.84	34.946	34.946	2.683	24.388	24.388
2	2.215	20.134	55.08	2.22	20.134	55.08	2.469	22.447	46.835
3	1.197	10.877	65.958	1.2	10.877	65.958	2.104	19.123	65.958
4	0.903	8.205	74.163						
5	0.897	8.156	82.318						
6	0.603	5.484	87.802						
7	0.529	4.813	92.616						
8	0.305	2.776	95.392						
9	0.236	2.147	97.54						
10	0.14	1.27	98.81						
11	0.131	1.19	100						

NOTE: Extraction Method: Principal Component Analysis.

The eigenvalues and percent of explained variance for all possible factors is illustrated in Table 9. Only the first three factors (components) demonstrated eigenvalues greater than 1. Together, these three factors explained 65.96% of the total variance. Only rotational calculations for these three factors were calculated.

Because the factor scores will be used in other analyses, it was important to use orthogonal rotation methods to assure that the resulting factor scores are not correlated with other factors; thus avoiding problems with multicollinearity assumptions in multivariate statistical procedures. Varimax rotation was calculated to simplify interpretation of the factors. As shown in Table 9,

the rotation procedure does not change the percent of explained variance; it only affects the distribution of the variance on each factor.

Next, the rotated component matrix was examined to evaluate and name the extracted factors (Table 10). Factor loadings represent the correlation between scores of individual measures and each of the factors. The first factor was named “Situation-Caregiver” because it represented the largest loading for the NPI Occupational disruptiveness subscale. It also contained high loadings of the FAC cognitive status, and NPI delusions, hallucinations, motor behavior, and irritability subscales. The second factor was named “Psychological” and contained high loadings for NPI depression, anxiety, delusions, disinhibition, motor behavior, irritability, and occupational disruptiveness subscales. The third factor was named “Physical-Cognitive” and contained high loadings for the inverse SIB scores, FAC cognitive status and inappropriate behavior subscales, and NPI depression subscale. Because several variables were significantly loaded onto more than one factor, a simple structural solution was not achieved.

Table 10. *Rotated Component Matrix: Predictor Variables*

Variable	Component		
	1	2	3
NPI Occupational disruptiveness	0.652	0.614	
NPI Depression		0.370	-0.598
NPI Anxiety		0.820	
NPI Delusions	0.667	0.444	
NPI Hallucinations	0.901		
NPI Disinhibition		0.805	
FAC Inappropriate behavior			0.887
NPI Motor Behavior	0.570	0.455	
NPI Irritability	0.665	0.304	
FAC Cognitive Status	0.358		0.520
SIB (Inverse)			0.801

NOTE: Neuropsychiatric Inventory (NPI); Functional Assessment Checklist (FAC); Severe Impairment Battery (SIB). Extraction Method: Principal Component Analysis; Rotation Method: Varimax with Kaiser Normalization. Small factor loadings >0.3 are suppressed.

The magnitude of the rotation applied to the original factors to obtain the rotated factor solution was surveyed in the Component Transformation Matrix. By examining the scores outside of the center diagonal (scores 1, 1; 2, 2; 3, 3) it was determined that the rotation for components one and two were large with all rotations above 0.5. Component 3 was calculated with a small rotation because all transformations in column 3 were below 0.5.

Agitation. Agitation was measured by the CMAI, FAC agitation subscale, and NPI agitation subscale. There were 48 complete cases available for analysis. The KMO Measure of sampling adequacy was at the low, but acceptable (KMO = .59). Bartlett's Test of Sphericity was significant only at the .05 level ($\chi^2 = 10.146, p = .017$), indicating that the data may not be perfectly suited for exploratory factor analysis, but still acceptable. There was also a moderate correlation between FAC agitation and CMAI scores (Table 6: $r = .39, p < .01$), further supporting the application of exploratory factor analysis.

The communalities of extracted variance shown in Table 11 indicate that the NPI agitation subscale had the least variance explained by the factor analysis (37.6%). The FAC agitation subscale and CMAI had similar percentages of variance explained by the extracted factor. Table 12 illustrates that only one factor was extracted. This factor explained only 51.69% of the total variance of all three measures. Factor rotation was not possible as only one factor was calculated.

Table 11. *Communalities between Agitation Measures*

	Initial	Extraction
FAC Agitation subscale	1.000	.578
NPI Agitation subscale	1.000	.376
CMAI	1.000	.596

NOTE: Functional Abilities Checklist (FAC); Neuropsychiatric Inventory (NPI); Cohen-Mansfield Agitation Inventory (CMAI).
Extraction Method: Principal Component Analysis.

Table 12. *Total Variance Explained: Agitation Factor*

Component	Initial Eigenvalues			Extraction Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	1.551	51.694	51.694	1.551	51.694	51.694
2	0.824	27.477	79.171			
3	0.625	20.829	100.000			

NOTE: Extraction Method: Principal Component Analysis.

The factor loading of each of the three agitation measures on the single extracted factor is shown in Table 13. The correlation of the NPI agitation subscale and the extracted factor was .61. The FAC agitation subscale and CMAI each had higher factor loadings, indicating a higher correlation between these measures and the factor score.

Table 13. *Agitation Component Matrix*

	Component 1
FAC Agitation subscale	0.761
NPI Agitation subscale	0.613
CMAI	0.772

NOTE: Functional Abilities Checklist (FAC); Neuropsychiatric Inventory (NPI); Cohen-Mansfield Agitation Inventory (CMAI).

Extraction Method: Principal Component Analysis. One component extracted.

Performance Outcomes. The functional abilities aspect of the performance outcome theoretical concept was measured by the FAC self-care subscale and GDS/FAST scale. There were 48 complete cases available for analysis. Other measures of functional performance were not included in the analysis because of the lack of overlapping cases. The KMO Measure of sampling adequacy was at the lowest range of acceptable values ($KMO = .50$). Bartlett's Test of Sphericity was significant ($\chi^2 = 12.25, p < .001$), indicating that the data are acceptable for exploratory factor analysis. There was a moderate correlation between FAC self-care and GDS/FAST scores (Table 7: $r = .43, p < .001$).

The communalities of extracted variance indicate that both measures of functional ability had 71% of their variances explained by the extracted factor (named Functional Performance factor). Table 14 illustrates that the single factor describing both measures accounted for 71% of the total explained variance. Factor rotation was not possible as only one factor was calculated. Finally, the component matrix indicated that both the FAC self-care subscale and GDS/FAST scores had a factor loading of .844. This factor loading shows that the correlation between original FAC self-care and GDS/FAST scores had a correlation of .84 with the extracted factor.

Table 14. *Total Variance Explained: Performance Outcome Factor*

Component	Initial Eigenvalues			Extraction Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	1.425	71.251	71.251	1.425	71.251	71.251
2	0.575	28.749	100.000			

NOTE: Extraction Method: Principal Component Analysis.

Path Analysis

Before analyzing the path analysis, the data were checked against the assumptions for path analysis. Path analysis has several assumptions in common with multiple regression, as well as unique assumptions for path analysis. Theoretically-based assumptions that are unique to this method include the assumption that the independent and dependent variables are correlated, independent variables occur before dependent variables in time, and that the relationship between independent and dependent variables is nonspurious and does not disappear when effects of additional variables are controlled (Munro, 2005). The first two assumptions are met through the theory that guided the construction of the model; the third assumption is difficult to confirm with certainty because all possible confounding variables cannot be measured with certainty.

Statistically-based assumptions for path analysis also assume that correlated, independent variables have a relationship that is represented by the size of their correlation coefficients, since these relationships cannot be directly measure with this method (Munro, 2005). Since independent variables were rotated factors, their correlation was zero and the assumption was met. The model is assumed to be recursive: it moves only in one direction (Munro, 2005). This assumption was met by all proposed relationships moving from the independent variables toward the dependent variables. Variables should include interval level data, although occasionally dummy-coded data can be acceptable (Munro, 2005). In this analysis, all variables were measured on ratio and interval level scales. Finally, path analysis assumes that all variables are measured without error (Munro, 2005). The data included in this model approached a lack of measurement error as no outliers were observed and all measures had good psychometric properties.

Statistical assumptions are identical to assumptions of regression analysis (Munro, 2005). It is assumed that relationships between the exogenous and endogenous variables are linear, and other patterns of relationships are not interpreted. Residual differences between observed values and values predicted by the line of regression are not correlated with other residual values and also not correlated with exogenous variables in the model.

Using the factors calculated above, the path model following the TOUS was constructed and tested (see Figure 5). The goodness-of-fit between the model and the data was evaluated with a chi-square test. The null hypothesis stated that the model was consistent with the data. The chi-square of Model A was statistically significant and the null hypothesis was rejected; the model was not a good fit for the data ($\chi^2 = 24.68$, $df = 3$, $p < .001$).

To identify a better fitting model, the analysis was modified to include direct paths between predictors and Functional Performance. A strong relationship was found between the predictor Physical: Cognitive factor and Functional Performance outcome factor. The fit of Model A was improved upon by adding the direct effects of the predictor Physical: Cognitive factor to the Functional Performance factor as the outcome (see Figure 6). The chi-square results of this model indicate that the null hypothesis could not be rejected and Model B is consistent with the data ($\chi^2 = 2.418$, $df = 2$, $p = .299$).

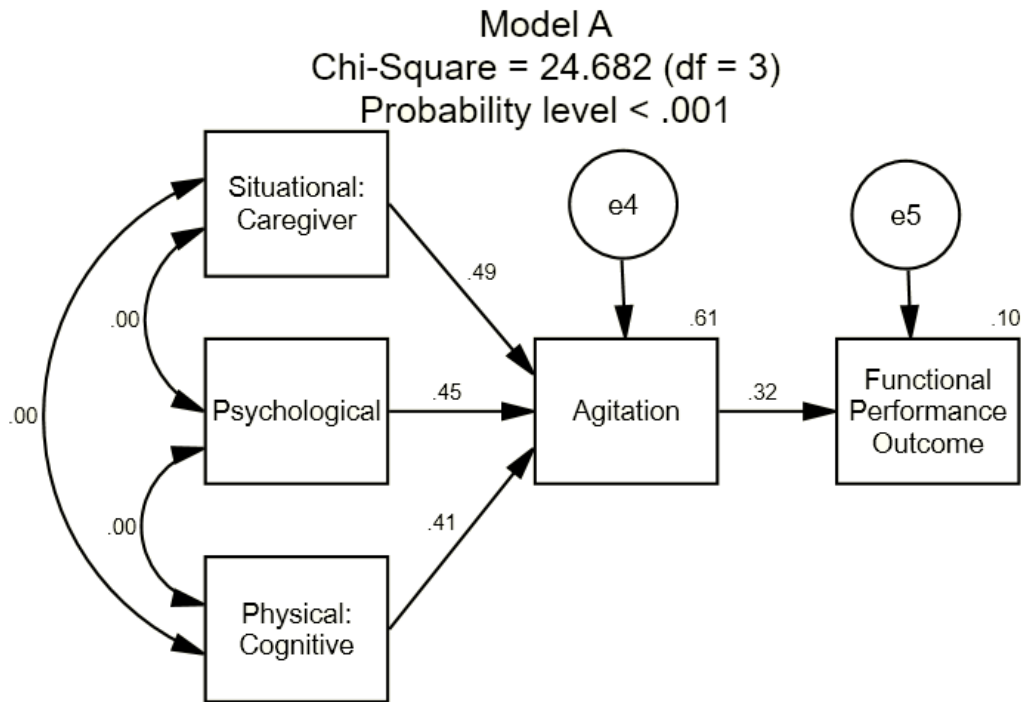


Figure 5. Path Model A

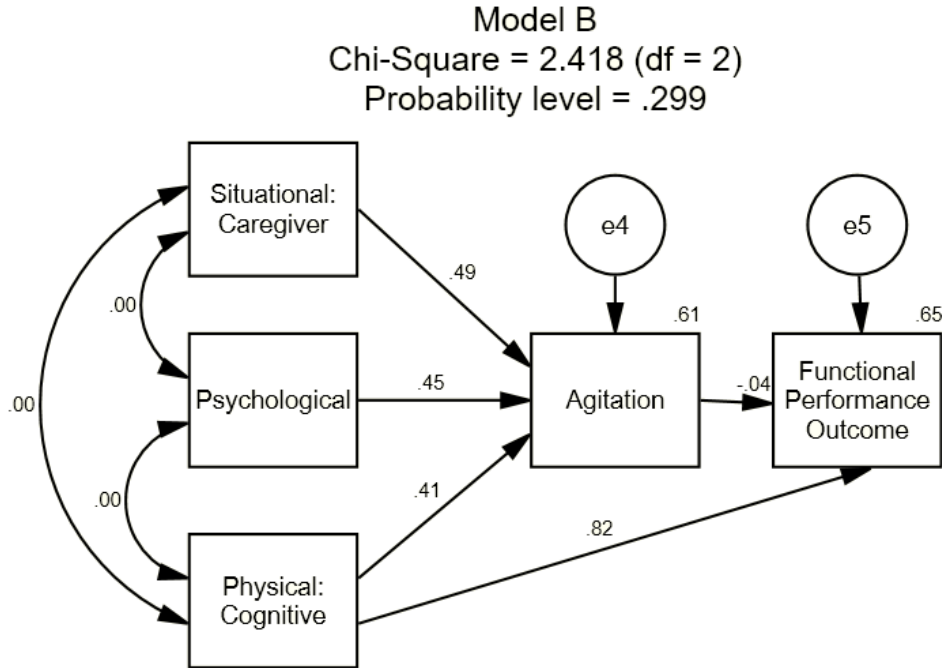


Figure 6. Path Model B

According to Pedhazur (1982), larger probabilities for the chi-square goodness-of-fit test indicate the best fitting model. To explore if the model could be further optimized to fit the data, two additional paths were investigated. Since the only statistically nonsignificant path calculated in Model B was the path from Agitation to the Functional performance outcome, this path was removed. The resulting model, labeled Model C, is displayed in Figure 7. The removal of the path between Agitation and Functional Performance did increase p value of the statistical significance of the model compared to the first two iterations ($\chi^2 = 2.518$, $df = 3$, $p = .472$).

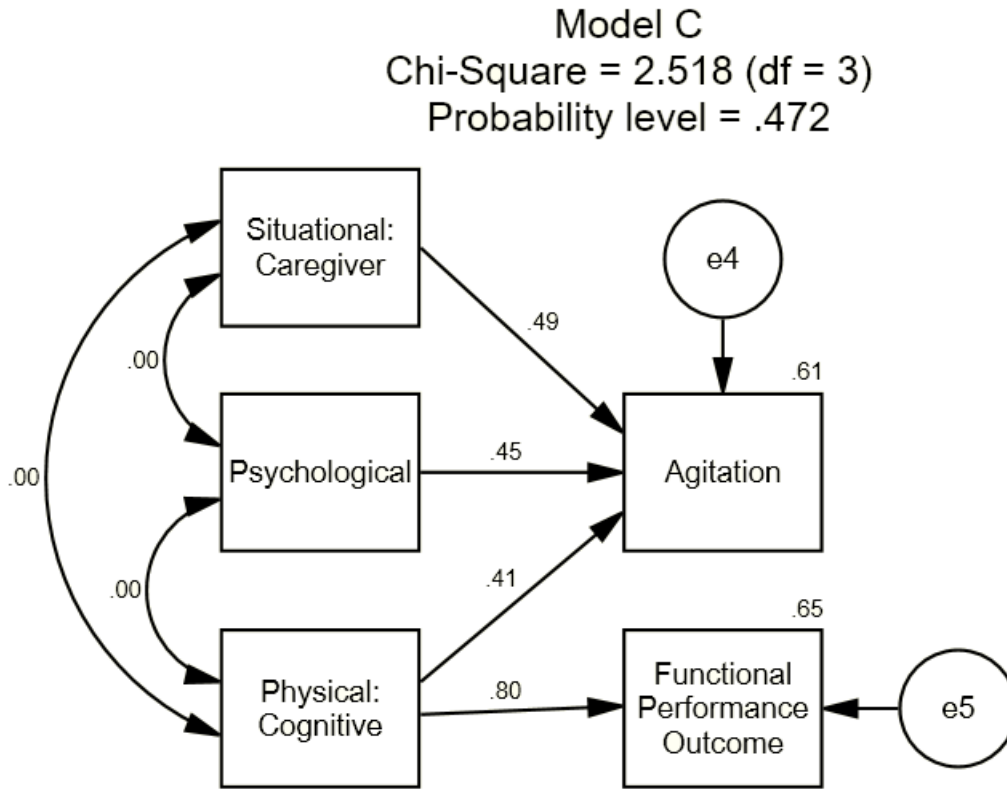


Figure 7. Path Model C

The model indices were then modified a final time to reverse the direction of the relationship between Agitation and Functional Performance. The final model, labeled Model D, is illustrated in Figure 8. Model D provided the best fit to the data ($\chi^2 = 1.049$, $df = 2$, $p = .592$). Further modifications resulted in no further improvements in model fit.

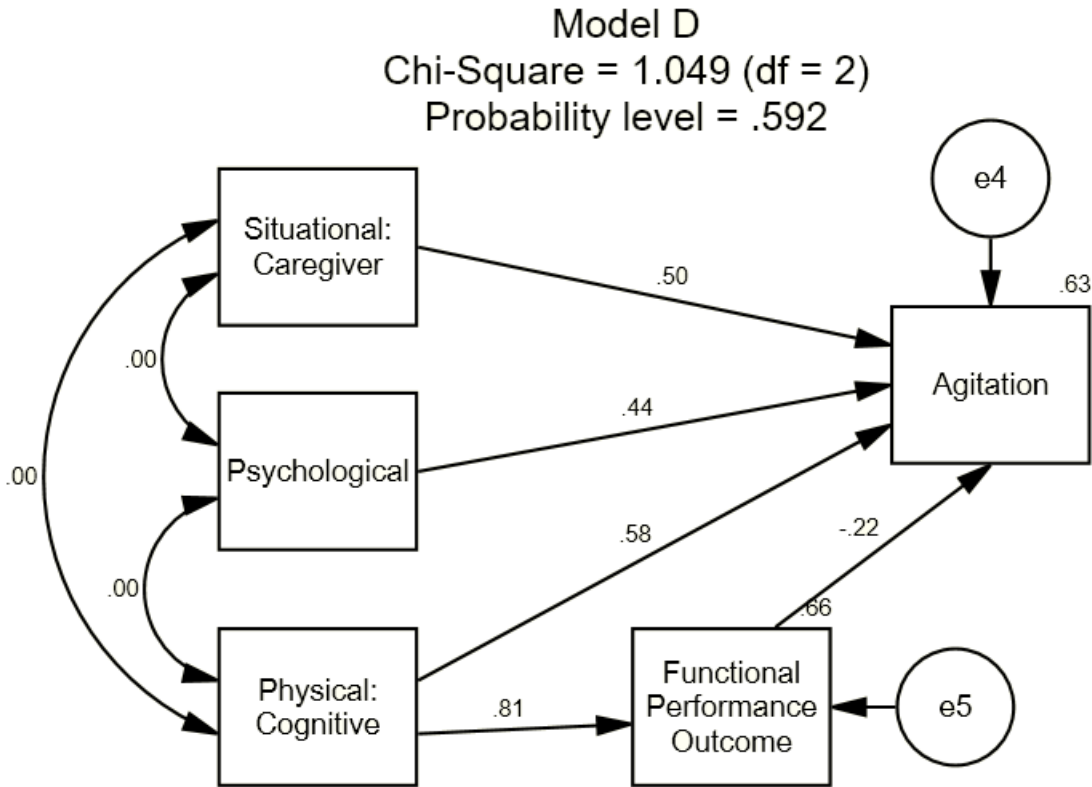


Figure 8. Path Model D

This final model partially supports the hypothesis of Aim 1. All three of the predicted antecedents to agitation are present in the final model, and have been assigned as interrelated predictors of agitation as described in the TOUS. The symptom of agitation is influenced by the situational, psychological, and physical antecedent factors, which is consistent with the relationship predicted by the TOUS. The outcome of function performance is present in the final model; however the model best fitting the data suggests that the relationship flows in the opposite direction as predicted by the TOUS. Rather than functional performance being the result of agitation, the model suggests that agitation is generally the result of greater functional impairment, although the exact relationship was not statistically significant. The regression coefficients derived from Model D are examined in detail in the following sections describing statistics for Aims 2 and 3.

Aim 2: Results of Statistical Analyses

Aim 2: Determine the effect of situational (physical and social environment), psychological (anxiety and depression), and physiological factors (comorbidities, pain, nutritional status, hearing, cognitive impairment, and fatigue) on agitation in persons with AD.

Hypothesis:

- (1) Supportive and stimulating physical and social environments will have a negative direct effect on agitation.
- (2) Comorbid psychological states will have a positive direct effect on agitation.
- (3) Comorbid physical conditions, pain, inadequate nutritional status, hearing loss, cognitive impairment, and fatigue will have a direct positive effect on agitation.

Aim 2 was tested with the examining the regression coefficients in the path analysis model best fitting the data. The magnitude, direction, and significance of the path coefficients from the situational, psychological, and physical factors to agitation are evaluated. Bivariate relationships (Pearson's correlation) between individual situational, psychological, and physical measures and the agitation measures are also examined to support these hypotheses.

Regression results from Path Analysis

The regression coefficients from the exogenous predictor variables (Situation-Caregiver, Psychological, and Physical-Cognitive factors) to Agitation and Agitation to Functional Performance are given in Table 15. Standardized path coefficients are used to allow for direct comparisons between different paths. All three of the exogenous predictor variables (Situation-Caregiver, Psychological, and Physical-Cognitive factors) have statistically-significant, positive effects on Agitation, supporting hypotheses 1, 2, and 3 of aim 1. Taken together, the predictors explain approximately 63% of the variance in Agitation ($R^2 = .628$).

Table 15. Path Coefficients for Predictors of Agitation

Outcome	Variables	Predictor	Unstandardized Coefficients			Standardized Coefficients	R ²
			B	S.E.	P	β	
Agitation	<---	Situation- Caregiver	0.509	0.09	< .001	0.504	
Agitation	<---	Psychological	0.446	0.09	< .001	0.442	
Agitation	<---	Physical- Cognitive	0.583	0.179	0.001	0.579	
Agitation	<---	Functional- Outcome	-0.207	0.18	0.251	-0.217	.628
Functional Outcome	<---	Physical- Cognitive	0.858	0.097	< .001	0.812	.660

NOTE: Standard Error = S.E.;

R² = Squared Multiple correlation for dependent variables.

Next, the paths were evaluated for direct, indirect, total, and spurious effects on agitation. The effects in table 16 were calculated with the decomposition of path correlations method (Smyth & Yarandi, 1992). Taking into consideration the indirect effect of the Physical-Cognitive factor on Agitation, it was determined that the strongest relationship was demonstrated in the effect of the Situation-Caregiver factor to the Agitation factor ($B = .509, p < .001$). Of note was the spurious component calculated from the product of the direct effects of Physical-Cognitive to Agitation and Physical-Cognitive to Functional Performance paths, added to the direct effect of Functional Performance on Agitation. This finding suggests that Functional Performance and Agitation have the Physical-Cognitive factor as a common cause.

Table 16. Direct, Indirect, and Total Effects on Agitation

Variable	Effect			
	Direct	Indirect	Total	Spurious
Situation-Caregiver	0.504	0	0.504	0
Psychological	0.442	0	0.442	0
Physical-Cognitive	0.579	-0.176	0.403	0
Functional Outcome	-0.217	0	-0.217	0.470

Other Analyses for Aim 2

Hypothesis 1. To further examine the hypothesis that supportive and stimulating physical and social environments will have a negative direct relationship with agitation, correlations between agitation measures (FAC agitation subscale, CMAI, and NPI agitation subscale) and individual measures of situation were examined in Table 17. For the 5 participants with both ZBI and CMAI scores measured, there was a very strong correlation between caregiver burden and cognitive impairment ($r = .96, p = .006$). The NPI occupational disruptiveness subscale was moderately correlated with both CMAI ($r = .55, p < .001$) and NPI agitation measures ($r = .58, p < .001$). Agitation as measured by the FAC was not correlated with any measures of the social environment. Caregiver reactions as measured by the MBPC subscales were not correlated with measures of agitation. This exploratory evidence from individual correlation calculations partially supported hypothesis 1 of aim 2: additional individual measures of caregiver burden were correlated with measures of agitation with the exception of the FAC agitation subscale and MBPC caregiver subscales in a small community sample.

Table 17. *Pearson Correlation of Agitation and Social Environment Measures*

Results: <i>r</i>	Agitation Measures		
	CMAI	FAC Agitation	NPI Agitation
Social Environment Measures			
Zarit Burden Interview Score	.956** n = 5	.a	.a
MBPC	.a	.274	.a
Memory and Behavior Caregiver reaction		n = 11	
MBPC	.a	.283	.a
ADL Caregiver reaction		n = 11	
NPI Occupational disruptiveness	.552** n = 48	.119 n = 48	.583** n = 48

NOTE: Memory and Behavior Problem Checklist-1987 (MBPC); Activities of Daily Living (ADL); Neuropsychiatric Inventory (NPI); Cohen Mansfield Agitation Inventory (CMAI); Functional Abilities Checklist (FAC), Hearing Handicap Inventory for Elderly Screening (HHIE-S).

** Correlation is significant at the 0.01 level (1-tailed).

.a = No comparative sample available.

Hypothesis 2. To further examine the hypothesis that the comorbid psychological states will have a positive direct relationship with agitation, correlations between psychological measures and agitation measures were examined in Table 18. The NPI depression ($r = .39, p = .007$) and anxiety ($r = .41, p = .004$) subscales had a weak association with CMAI. A moderate correlation was observed between the NPI delusion subscale and the CMAI ($r = .52, p < .001$); it also demonstrated a weak correlation with the NPI agitation subscale ($r = .36, p = .011$). NPI hallucinations subscale was weakly correlated with the NPI agitation subscale ($r = .40, p = .004$). The NPI disinhibition ($r = .59, p < .001$) and aberrant motor behavior subscales ($r = .50, p < .001$) both demonstrated a moderate relationship with the CMAI; NPI aberrant motor behavior was also weakly correlated with NPI agitation ($r = .29, p = .048$). NPI sleep subscale was weakly correlated with the FAC agitation subscale ($r = .31, p = .035$). The NPI irritability subscale demonstrated moderate correlation with both the CMAI ($r = .51, p < .001$) and the NPI agitation subscales ($r = .68; p < .001$). The ADAS non-cognitive behavioral subscale had a weak correlation with the FAC agitation subscale ($r = .47, p = .001$). The FAC inappropriate behavior subscale was weakly correlated with the NPI agitation subscale ($r = .29, p = .048$). No correlations were observed between NPI apathy or elation subscales and any measures of agitation.

Overall, the FAC agitation subscale had the fewest correlations with psychological measures. The CMAI and NPI agitation subscales were similarly correlated with psychological measures. Only the NPI delusions, aberrant motor behavior, and irritability subscales were correlated with more than one measure of agitation. This exploratory evidence from individual correlation calculations partially supported hypothesis 2 of aim 2: most individual measures of comorbid psychological states were correlated with at least one measure of agitation.

Table 18. *Pearson Correlations of Agitation and Psychological Measures*

Results: <i>r</i>	Agitation Measures		
	CMAI	FAC Agitation	NPI Agitation
Psychological Measures			
NPI Depression	.385** n = 48	-.098 n = 48	-.051 n = 48
NPI Anxiety	.410** n = 48	.064 n = 48	.110 n = 48
NPI Apathy	-.222 n = 48	-.076 n = 48	.114 n = 48
NPI Delusions	.518** n = 48	.134 n = 48	.362* n = 48
NPI Hallucinations	.213 n = 48	-.015 n = 48	.404** n = 48
NPI Elation	-.057 n = 48	.144 n = 48	.095 n = 48
NPI Disinhibition	.588** n = 48	.267 n = 48	.062 n = 48
NPI Aberrant Motor Behavior	.503** n = 48	.171 n = 48	.287* n = 48
NPI Sleep	.241 n = 48	.305* n = 48	.116 n = 48
NPI Irritability	.508** n = 48	.176 n = 48	.676** n = 48
ADAS Non-cognitive Behavioral	.251 n = 30	.465** n = 51	.205 n = 30
FAC Inappropriate behavior	.135 n = 59	.210 n = 81	.287* n = 48

NOTE: Cohen-Mansfield Agitation Inventory (CMAI); Functional Abilities Checklist (FAC); Neuropsychiatric Inventory (NPI); Alzheimer Disease Assessment Scale (ADAS).

* Correlation is significant at the 0.05 level (1-tailed).

** Correlation is significant at the 0.01 level (1-tailed).

Hypothesis 3. Correlations between physical measures and agitation measures were examined in Table 19 to further examine the hypothesis that physical aspects of health including comorbid physical conditions, pain, inadequate nutritional status, hearing loss, cognitive impairment, and fatigue have a direct, positive relationship with agitation. There was a

moderately strong correlation between scores on Pain in Advanced Dementia measure and the CMAI ($r = .69, p = .001$). A strong inverse correlation was observed between MMSE and CMAI scores ($r = -.82, p = .045$). A weak inverse correlation was observed between and SIB scores and NPI agitation ($r = -.28; p = .028$). No correlations were observed between the FAC agitation subscale and any physical measures. No correlations were observed between agitation and CIRS-G, MNA, NPI appetite subscale, or the HHIE-S measures.

This exploratory evidence from individual correlation calculations partially supported hypothesis 3 of aim 2: few additional individual measures of comorbid physical conditions were correlated with measures of agitation. Individual measures of physical conditions were not correlated with more than one measure of agitation. Measures of cognitive impairment (MMSE and SIB) were correlated with agitation measures as identified in the path model. Additionally, only pain was identified as a physical measure correlated with agitation.

Table 19. *Pearson Correlations of Agitation and Physical Measures*

Results: <i>r</i>	Agitation Measures		
	Cohen-Mansfield Agitation Inventory	FAC Agitation subscale	NPI Agitation subscale
Cumulative Illness Rating Scale-Geriatrics	.199 n = 18	-.150 n = 13	.006 n = 13
Pain AD	.689** n = 18	.263 n = 13	.334 n = 13
Mini Nutritional Assessment	-.104 n = 18	-.021 n = 13	.107 n = 13
NPI Appetite subscale	-.066 n = 48	-.187 n = 48	.058 n = 48
HHIE-S	.030 n = 5	.a	.a
Mini Mental State Exam Composite	-.818* n = 5	.a	.a
Severe Impairment Battery	-.102 n = 66	-.173 n = 67	-.279* n = 48

NOTE: Cohen-Mansfield Agitation Inventory (CMAI); Functional Abilities Checklist (FAC); Neuropsychiatric Inventory (NPI); Hearing Handicap Inventory for the Elderly – Short Form (HHIE-S); Alzheimer Disease Assessment Scale (ADAS).

* Correlation is significant at the 0.05 level (1-tailed).

** Correlation is significant at the 0.01 level (1-tailed).

.a = No comparative sample available.

Aim 3:

Aim 3: Determine the effect of situational, psychological, physical antecedent factors and agitation on performance outcomes (functional status and quality of life) in persons with AD.

Hypothesis:

- (1) Supportive and stimulating physical and social environments will have an indirect positive effect on functional status and quality of life through reduced agitation.

- (2) Comorbid psychological states will have an indirect negative effect on functional status and quality of life through increased agitation.
- (3) Comorbid physical conditions, pain, nutritional status, hearing loss, cognitive impairment, and fatigue will have an indirect negative effect on functional status through increased agitation.
- (4) Agitation will have a negative direct effect on functional status and quality of life.

Aim 3 is tested by examining the regression coefficients in the path analysis model best fitting the data. The magnitude, direction, and significance of the path coefficients from situational, psychological, and physical factors to functional ability are evaluated. The paths from agitation to functional ability are also examined. Bivariate relationships (Pearson's correlation) between individual measures and the functional performance outcome were also examined to test these hypotheses.

Regression results from Path Analysis

The regression coefficients from the exogenous predictor Physical-Cognitive factor to the Functional Performance factor and from the Functional Performance Factor to Agitation are given in Table 15. This model indicated that only the Physical-Cognitive exogenous predictor factor had a significant effect on the Functional Performance factor ($B = 0.858, p < .001$). The direct effect of the Physical-Cognition factor on the Functional Performance factor explained about 66% of the variance in Functional Performance ($R^2 = .660$). This finding supports hypothesis 3 to the extent that the Physical-Cognition factor has an effect on Functional Performance, but provides evidence against hypothesis 1 and 2 as no relationships between Situation-Caregiver or Psychological factors and the Functional Performance factor were found.

The path model suggests that there is no important relationship between agitation and functional performance ($B = -0.207$, $p = .47$; Table 15). Rather, the path model indicates that both agitation and functional performance are the result of the Physical-Cognitive factor (spurious effect $B = .470$; Table 16). Hypothesis 4 is not supported by these data.

Additional Analyses to test Aim 3:

Hypothesis 1. Correlations were calculated between situational measures and measures of functional outcomes to explore the hypothesis that supportive and stimulating physical and social environments will have a positive relationship with functional status and quality of life (Table 20). Zarit Burden Inventory was strongly correlated with GDS/FAST scores ($r = .83$, $p = .042$), and also had a strong negative correlation with ADRQL scores ($r = -.93$; $p = .013$) in the 5 participants who had all measures. The MBPC caregiver reaction to ADL subscale was weakly correlated with the MBPC ADL subscale ($r = .34$, $p = .028$). No correlations were observed between MBPC or NPI occupational disruptiveness scales and measures of functional performance outcomes. Overall, exploratory evidence from individual correlation calculations partially supported hypothesis 1 of aim 3: additional individual measures of caregiver burden were correlated with measures of functional status and quality of life.

Table 20. Pearson Correlations of Functional Performance and Situational Measures

Results: <i>r</i>	Functional Status Measures			Quality of Life Measures		
	FAC Self-care	GDS/FAST	MBPC ADL	ADRQL	QOL AD	Health Survey SF-36v2
Zarit Burden Interview Score	.a	.828* n = 5	.a	-.923* n = 5	-.310 n = 5	-.100 n = 5
MBPC Memory and Behavior Caregiver reaction subscale	-.031 n = 11	.303 n = 28	.143 n = 28	.a	.a	.a
MBPC ADL Caregiver reaction subscale	-.059 n = 11	.284 n = 28	.341* n = 28	.a	.a	.a
NPI Occupational disruptiveness subscale	.023 n = 48	.111 n = 30	.a	.a	.a	.a

NOTE: Memory and Behavior Problem Checklist-1987 (MBPC); Activities of Daily Living (ADL); Neuropsychiatric Inventory (NPI); Cohen Mansfield Agitation Inventory (CMAI); Functional Abilities Checklist (FAC), Global Deterioration Scale/Functional Assessment Staging Tool (GDS/FAST). Alzheimer Disease Related Quality of Life (ADRQL), Quality of Life in Alzheimer Disease (QOLAD)

* Correlation is significant at the 0.05 level (1-tailed).

** Correlation is significant at the 0.01 level (1-tailed).

.a = No comparative sample available.

Hypothesis 2. Correlations were calculated between psychological measures and measures of functional outcomes to explore the hypothesis that comorbid psychological states will have a negative relationship with functional status and quality of life (Table 21). A weak correlation was measured between NPI apathy and FAC self-care subscales ($r = .30, p = .018$). A weak correlation was also measured between the ADAS non-cognitive behavioral and FAC self-care subscale ($r = .32, p = .010$). The FAC inappropriate behavior subscale was moderately correlated with both the FAC self-care subscale ($r = .41, p < .001$) and GDS/FAST scores ($r = .49, p < .001$).

Table 21. *Pearson Correlations of Functional Performance and Psychological Measures*

Results: <i>r</i> Psychological Measures	Functional Status Measures			Quality of Life Measures		
	FAC Self-care	GDS/FAST	MBPC ADL	ADRQL	QOL- AD	Health Survey SF-36v2
NPI Depression	-.126 n = 48	-.062 n = 30	.a	.a	.a	.a
NPI Anxiety	.021 n = 48	-.051 n = 30	.a	.a	.a	.a
NPI Apathy	.303* n = 48	.241 n = 30	.a	.a	.a	.a
NPI Delusions	-.001 n = 48	.024 n = 30	.a	.a	.a	.a
NPI Hallucinations	.021 n = 48	.007 n = 30	.a	.a	.a	.a
NPI Elation	.201 n = 48	-.046 n = 30	.a	.a	.a	.a
NPI Disinhibition	-.084 n = 48	-.058 n = 30	.a	.a	.a	.a
NPI Aberrant motor behavior	.095 n = 48	.208 n = 30	.a	.a	.a	.a
NPI Sleep	.043 n = 48	-.032 n = 30	.a	.a	.a	.a
NPI Irritability	.129 n = 48	.036 n = 30	.a	.a	.a	.a
ADAS Non-cognitive behavioral	.324* n = 51	.133 n = 52	.271 n = 10	.a	.a	.a
FAC Inappropriate behavior	.408** n = 81	.485** n = 62	-.083 n = 11	.a	.a	.a

NOTE: Cohen-Mansfield Agitation Inventory (CMAI); Functional Abilities Checklist (FAC); Neuropsychiatric Inventory (NPI); Alzheimer Disease Assessment Scale (ADAS) Memory and Behavior Problem Checklist-1987 (MBPC); Activities of Daily Living (ADL); Neuropsychiatric Inventory (NPI); Global Deterioration Scale/Functional Assessment Staging Tool (GDS/FAST). Alzheimer Disease Related Quality of Life (ADRQL), Quality of Life in Alzheimer Disease (QOL-AD).

* Correlation is significant at the 0.05 level (1-tailed).

** Correlation is significant at the 0.01 level (1-tailed).

.a = No comparative sample available

No correlations were found between functional status measures and NPI depression, anxiety, delusions, hallucinations, elation, disinhibition, aberrant motor behavior, sleep, or irritability subscales. Comparative samples were not available to calculate correlations for measures of

quality of life. MBPC ADL scores could only be compared to ADAS non-cognitive behavioral and FAC inappropriate behavior subscales, though no correlations were found. In general, this exploratory evidence from individual correlation calculations demonstrates further evidence against hypothesis 2 of aim 3: additional individual psychological measures were not well correlated with measures of functional status with the exception correlations between functional status and general measures of AD-related behavioral symptoms (ADAS non-cognitive behavioral subscale and FAC Inappropriate behavior subscale) and the NPI apathy subscale.

Hypothesis 3. Correlations were calculated between physical measures and measures of functional outcomes to explore the hypothesis that comorbid physical conditions, pain, nutritional status, hearing loss, cognitive impairment, and fatigue will have a negative relationship functional status and quality of life (Table 22). CIRS-G scores were moderately to highly correlated with FAC self-care ($r = .60, p = .015$), and GDS/FAST functional status measures ($r = .93; p = .011$). CIRS-G scores had a strong inverse correlation with the ADRQL measure of quality of life ($r = -.93, p = .011$) for the 5-13 participants with measurements. Nutritional status measured by the MNA was strongly correlated with QOLAD measures ($r = .90, p = .019, n = 5$). Hearing scores were strongly correlated with quality of life measured on the SF-36 ($r = .83, p = .042, n = 5$). Mini mental state exam scores had a strong inverse correlation with GDS/FAST measures of functional status ($r = -.84, p = .036, n = 5$), and were strongly correlated with quality of life as measured by the ADRQL ($r = .91, p = .017, n = 5$). Cognition as measured by the SIB had a moderate inverse correlation with FAC self-care ($r = -.57, p < .001, n = 67$) and GDS/FAST functional status measures ($r = -.54, p = .015, n = 53$), and a very strong positive relationship with ADRQL ($r = .97, p = .004, n = 5$).

Correlations between Pain AD and the NPI appetite subscale with measures of functional performance outcomes and were not observed. Correlations between physical measures and the MBPC ADL subscale could not be calculated due to lack of overlapping participants. Many of the correlations that were observed were based on small samples of less than 15 participants and should be interpreted with caution. The results of these exploratory analyses provided evidence that partially supported hypothesis 3 of aim 3: some individual measures of comorbid physical conditions were correlated with measures of functional status and quality of life.

Table 22. *Pearson Correlations of Functional Performance and Physical Measures*

Results: <i>r</i> (<i>p</i>)	Functional Status Measures			Quality of Life Measures		
	Physical Measures	FAC Self-care	GDS/FAST	MBPC ADL	ADRQL	QOL AD
CIRS-G	.603* n = 13	.931* n = 5	.a	-.931* n = 5	.192 n = 5	-.395 n = 5
PainAD	.210 n = 13	-.691 n = 5	.a	.475 n = 5	.140 n = 5	-.155 n = 5
MNA	-.441 n = 13	-.085 n = 5	.a	.113 n = 5	.899* n = 5	-.694 n = 5
NPI Appetite subscale	.010 n = 48	-.025 n = 30	.a	.a	.a	.a
HHIE-S	.a	-.250 n = 5	.a	.255 n = 5	-.215 n = 5	.826* n = 5
Mini Mental State Exam	.a	-.844* n = 5	.a	.908* n = 5	-.344 n = 5	.617 n = 5
Severe Impairment Battery	-.572** n = 67	-.543** n = 53	.a	.967** n = 5	.300 n = 5	.098 n = 5

NOTE: Cumulative Illness Rating Scale-Geriatrics (CIRS-G); Mini Nutritional Assessment (MNA); Neuropsychiatric Inventory (NPI); Hearing Handicap Inventory for the Elderly – Short Form (HHIE-S); Severe Impairment Battery (SIB); Functional Abilities Checklist (FAC); Global Deterioration Scale/Functional Assessment Staging Tool (GDS/FAST); Memory and Behavioral Problems Checklist, Activities of Daily Living (MBPC ADL); Alzheimer Disease Related Quality of Life (ADRQL), Quality of Life in Alzheimer Disease (QOLAD).

* Correlation is significant at the 0.05 level (1-tailed).

** Correlation is significant at the 0.01 level (1-tailed).

.a = No comparative sample available.

Hypothesis 4. Correlations were calculated between agitation measures and measures of functional performance to explore the hypothesis that agitation will have a negative relationship functional status and quality of life (Table 23). Weak correlations were found between the CMAI and GDS/FAST measure of functional status ($r = .31$; $p = .018$, $n = 47$), as well as a strong inverse relationship between the CMAI and ADRQL ($r = -.96$, $p = .006$, $n = 5$). The FAC agitation subscale had a weak correlation with the FAC self-care subscale ($r = .19$, $p = .040$, $n = 83$). Agitation measured by the NPI agitation subscale had no significant correlations with functional status measures, although the weak correlation with the FAC self-care subscale approached significance ($r = .23$, $p = .057$, $n = 5$). Correlation calculations were limited by small sample size for quality of life measures with little overlap in observed participants. This evidence from individual correlation calculations partially supported hypothesis 4 of aim 1: some individual measures of agitation were correlated with individual measures of functional status and quality of life.

Table 23. *Pearson Correlations of Functional Performance and Physical Measures*

Physical Measures	Functional Status Measures			Quality of Life Measures		
	FAC Self-care	GDS/FAST	MBPC ADL	ADRQL	QOL-AD	Health Survey SF-36v2
CMAI	.042 n = 61	.306* n = 47	.a	-.955** n = 5	.192 n = 5	-.106 n = 5
FAC Agitation	.193* n = 83	-.165 n = 64	.250 n = 11	.a	.a	.a
NPI Agitation	.231 n = 48	.131 n = 30	.a	.a	.a	.a

NOTE: Cohen-Mansfield Agitation Inventory (CMAI); Functional Abilities Checklist (FAC); Neuropsychiatric Inventory (NPI); Hearing Handicap Inventory for the Elderly – Short Form (HHIE-S); Alzheimer Disease Assessment Scale (ADAS), Global Deterioration Scale/Functional Assessment Staging Tool (GDS/FAST). Alzheimer Disease Related Quality of Life (ADRQL), Quality of Life in Alzheimer Disease (QOLAD).

*. Correlation is significant at the 0.05 level (1-tailed).

**. Correlation is significant at the 0.01 level (1-tailed).

.a = No comparative sample available.

CHAPTER 5: DISCUSSION

The central purpose of this dissertation was to test a model of agitated behavioral symptoms in persons with Alzheimer disease within the framework defined by the Theory of Unpleasant Symptoms (TOUS; Lenz et al., 1995). Specifically, this dissertation sought to (1) describe the phenomenon of agitated behavioral symptoms in persons with AD within the constructs predicted in the TOUS; (2) to investigate the relationships between situational, psychological, and physiological factors on agitated behavioral symptoms in persons with AD; and (3) to investigate the relationships between functional performance outcomes and situational, psychological, and physiological factors and agitated behavioral symptoms. To a large extent, the TOUS was found to accurately predict most (though not all) of the observed relationships.

This discussion is divided into three main sections. The first section describes the conclusions drawn from study results and compares them to expected findings from extant literature. Second, limitations of the results interpretation and study methods are discussed. The chapter concludes with recommendations for future research.

Research Conclusions

Support for the Theory of Unpleasant Symptoms

The TOUS is a middle-range theory developed to guide research and practice around a variety of unpleasant symptom experiences (Lenz et al., 1997). It was originally developed to describe linear relationships between influential factors, symptoms, and outcomes (Lenz & Gift, 1998). Later, authors expanded the TOUS to more broadly consider interrelationships between predictors and reciprocal interactions between symptoms, outcomes and predictors. Therefore, the original version of the TOUS was selected to guide the hypotheses and path model in the present study. The TOUS defined variables of interest by category and relationship to

symptoms. Main study results pertaining to the variables and relationships hypothesized by the TOUS are discussed first, followed by a discussion of results by individual variables.

Variables. Overall, the TOUS provided a good framework for identifying and categorizing variables that may affect agitation. The antecedent category contained three types of variables (physiologic, psychologic, and situational) that are thought to influence a single symptom (agitation) that is measured by its distress, duration, intensity, and quality. The performance outcome category includes functional status, and was theorized to be affected by the symptom. These variables were all represented to some extent within the final path model.

Situation-Caregiver. This study measured the antecedent concepts with eleven instruments. The exploratory factor analysis identified three factors summarizing the instruments that corresponded to the three antecedent categories proposed by the TOUS. The concept of situational antecedents paralleled to the factor named Situation-Caregiver. The Situation-Caregiver factor included occupational disruption measured on the NPI as well as measures of delusions, and partially measured hallucinations, aberrant motor behavior, irritability, and cognitive status measured by the FAC.

The NPI occupational disruptiveness scale has previously been applied to the measurement of caregiver burden, especially for professionals caring for those with AD in institutional settings (Tan, Wong, & Allen, 2005). In such environments, the NPI Occupational Disruptiveness (OD) subscale measures staff burnout that results in added costs, staff turnover, and impedes optimal care (Tan et al., 2005). Outward expressions of hallucinations, delusions, irritability, and aberrant motor behaviors rather than inward depression, anxiety or cognitive decline aggravate caregiver burden, which supports the identification of these outward and inward variables into separate factors (Hiyoshi-Taniguchi, Becker, & Kinoshita, 2018; Reed et

al., 2020; Tan, 2005). The FAC cognitive status subscale was not expected to be loaded onto the caregiver burden factor as previous studies have found cognition to be unrelated to caregiver burden (Reed et al., 2020). Although the FAC cognitive status scale loaded minimally onto the Situation-Caregiver factor, it loaded more strongly onto the Physical-Cognitive factor.

Psychological. The Psychological factor was primarily defined by NPI anxiety, depression, and disinhibition with minor loadings of occupational disruptiveness, delusions, motor behavior, and irritability. This factor structure is generally consistent with symptom cluster “emotion and disinhibition” which includes depression and disinhibition identified by Nagata and colleagues (2016). The variables describing the Psychological factor are also consistent with AD-related impairments of the neural networks connecting with the angular cingulate cortex which is thought to cause deficits in emotional regulation and impulse control (dos Santos Tascone & Bottino, 2013).

Physical-Cognitive. The final predictor factor was named Physical-Cognitive and was defined by the SIB scores, FAC cognitive status, FAC inappropriate behaviors, and had a negative factor load for NPI depression. It is possible that some of the items on the FAC inappropriate behavior subscale measure such a broad range of behaviors that many overlap with signs of diminished cognition. Because depression is a risk factor for developing AD as well as an early sign of the disease, the negative loading of depression on the Cognitive-Physical factor was surprising (Defrancesco et al., 2017). An explanation for the negative loading of depression on the cognition factor is that individuals with very advanced AD no longer express depression in a way that is immediately recognizable as their capacity for complex communication declines, and therefore less depression may be reported during late-stage disease when impaired cognition is most pronounced.

Although the TOUS originally conceptualized cognitive functioning as a component of performance outcome, its position was modified in this study. Because diminishing cognition is an expected consequence of the physical neurodegeneration in AD, it was conceptualized here as an indicator of the physiologic antecedent concept. Hutchinson and Wilson (1998) reached a similar conclusion about blurred theory components when applying the TOUS to interpreting qualitative data about behavioral symptoms in AD. Despite these minor conceptual challenges, work by Hutchinson and Wilson (1998) and this present study ultimately concluded that the TOUS remains useful in this population because of its emphasis on the complexity of interactions among symptoms.

Although the exploratory factor analysis of all of the variables measuring antecedent concepts did not achieve a simple structure with each measured indicator corresponding to a single factor, this is consistent with the description of the original TOUS model. For example, the TOUS identifies that social support contributes to both the psychological and situational concept (Lenz et al., 1995).

Agitation. The symptom of agitation was measured with three tools that considered each of the proposed aspects of the symptom experience: duration (frequency), distress, intensity (severity) and quality (specific agitated behaviors). The tools included the FAC agitation subscale, the NPI agitation subscale, and the CMAI. Although the term “symptom” is normally reserved for self-reported subjective experiences by individuals, the diminished cognition in AD reduces the reporting capability of individuals with AD. Therefore, symptoms in AD are generally reported by proxy observation of discernible behavioral signs of suspected symptoms (Hutchinson & Wilson, 1998).

Performance Outcome. Performance outcomes were measured by a factor containing the FAC self-care subscale and the FAST/GDS scores. The use of both tools was useful as the FAST/GDS scores individuals along an expected trajectory of the loss of ADLs over the disease course, while the FAC self-care subscale allowed more individualization of scores with questions about specific tasks that were difficult for participants and the frequency of these challenges (Reisberg, 1986; Swanson, Maas, & Buchwalter, 1994).

Relationships. The original TOUS defined simple, direct relationships between the three categories of antecedents (physiologic, psychologic, and situational) to a single symptom with one final direct relationship between the symptom and performance outcomes (Lenz et al., 1995). The first major finding from this study was that the path model guided by the TOUS was a good fit to the relationships in the observed data with one notable exception. The predicted relationship of a direct positive effect of agitation on functional impairment was not supported by the model. When the relationship between agitated behavioral symptoms and function performance outcomes were reversed, the optimal model for the data was produced. Although this arrangement produced the best-fitting model overall, the specific relationship between agitation and function was not statistically significant.

As predicted by the TOUS, the final model showed strong support for the relationships between situation and agitation, psychological symptoms and agitation, and physical health on agitated behavioral symptoms-. The model found no support for the effects of situational and psychological predictors on functional performance or the relationship between agitated behavioral symptoms and functional outcome. A relationship between physical predictors and functional outcome was supported. The spurious relationship calculated between agitation, functional outcome, and physical factors indicated that agitation and functional outcomes were

both the result of physical factors as opposed to any direct relationship between agitation and functional outcome.

One explanation for the lack of a significant relationship observed between agitated behavioral symptoms and performance outcomes could be attributed to an incomplete measurement of the performance outcome concept. While this study thoroughly measured functional ability with two distinct instruments, adequate sample was not available to consider quality of life indicators in the model. Functional status decline with AD progression is a consistent and expected finding, even with the most supportive care interventions (Reuben et al., 2019). It is possible that measurements of quality of life would provide a more stable measure of a modifiable performance outcome that is less directly tied to disease progression.

The consideration of important performance outcomes such as functional status and quality of life was seen as a major strength of the TOUS compared to other similar theories such as the needs-driven dementia-compromised behavior (NDB) framework (Algase et al., 1996), the unmet needs model (Cohen-Mansfield, 2000), and the Progressively Lowered Stress Threshold (PLST) model (Hall & Buckwalter, 1987). It may be possible that because of the all-encompassing nature of the AD degenerative process, a theory that is tailored to the experiences of this specific population would be more effective in conceptualizing relationships than a theory like TOUS which describes symptom experience regardless of specific population. Lenz and Gift (1998) report that the development of the TOUS was from a theory primacy approach starting with the clinical problem of symptom complaints across diverse clinical populations. Theories developed from the perspective of substantive area primacy are centered on the specific needs of unique patient populations, such as AD patients, and may be better tailored to describing the phenomenon of agitated behavioral symptoms in AD patients (Kim, 1996).

A path model to describe agitated behavioral symptoms in AD was previously reported by Chen and colleagues (2014). Chen's model was developed from the NDB framework and unmet needs model. There are several similarities between these models and the TOUS. All of the theoretical models include physical health, pain, psychological health, depression and environmental predictors that affect agitated behaviors (Algase et al., 1996, Cohen-Mansfield, 2000; Lenz et al., 1995). The biggest difference between the models is the conceptualization of cognitive impairment as a predictor of problematic behavioral symptoms in AD in the NDB and unmet needs models while the TOUS does not explicitly conceptualize AD-related cognitive decline as a predictor. The models also differ in the relationships between agitation and functional ability with NDB and unmet needs model categorizing functional ability as a predictor of agitation and TOUS considers it an outcome.

The path model identified by Chen et al. (2014), found that agitation was directly affected by cognitive function and depression. Indirect effects on agitation were found from pain and functional ability through depression. Functional ability was found to be affected by cognitive function and pain. The model identified in this study agreed with Chen's model to a large extent. Both models found agitation to be influenced by cognitive factors and psychological factors (including depression). Both models failed to find a direct relationship between functional ability and agitation (regardless of its hypothesized causative or outcome placement). Both models found that cognitive factors influenced both agitation and functional ability.

Key differences between the two models include the measured variables, study sample characteristics, explained variance, and the overall model fit. The model identified in the current study included additional measures of psychological states, caregiver-related situational factors, and multiple measures of agitation, but did not measure pain. Chen et al., (2014) included in

their study sample 405 older adults with dementia (not specifically AD), who resided in nursing homes in Taiwan. The sample from which this study's model was generated included 48 participants from community and institutional settings in Midwestern United States. The model generated in the present study explained nearly 63% of the variance in agitation while Chen's model explained only 11%. The model in this study also found that 66% of the variance in functional ability was explained by the cognitive factor while Chen's model found 52% of the variance in functional ability was explained by cognitive function and pain. Overall, both models fit their datasets, although the model generated in the present study had a better fit compared to Chen et al., (2014). Taken together, these models confirm the important impact of cognitive function and psychological factors on agitation. Our study adds the importance of the impact of caregiver burden on agitation.

With all of the strengths and weaknesses of the TOUS taken together, the fit between the data in this study and the TOUS is satisfactory in explaining the phenomenon of agitated behavioral symptoms in AD. When testing a theory to explain research data, the theory should aid the researcher in expanding knowledge and exploring a small part of the larger phenomenon of interest in depth (Artinian, 1988). It is not necessary that the theory explain all of the data but is more useful in the interpretation of some aspects. Especially when approaching a secondary analysis of data, the model is not expected to perfectly match the data since the theory was not used to guide instrument selection or to plan research methods (Lenz & Gift 1998). Regardless of these barriers, the TOUS provided a useful framework for formulating hypotheses and organizing the variables and relationships in the phenomenon of agitated behavioral symptoms in AD. The TOUS provided valuable insight to guide research exploration and to illuminate key

nursing interventions to improve care for this population. Further exploratory evidence within each variable category is discussed below.

Support for individual relationships

Situation. The effect of situational caregiver burden was found to have the greatest impact on agitation in the path model. This finding is consistent with previously reported research that negative interactions between overburdened caregivers and individuals with AD can worsen agitation severity in this population (de Mauléon et al., 2019; de Vugt et al., 2004; Ragneskog et al., 1998). The direction of the relationship is called into question by other findings that conceptualized caregiver burden as a result of agitation (Chiao, Wu, & Hsiao, 2015; Hiyoshi-Taniguchi et al., 2018). When viewed from a reciprocal-interactive perspective as outlined in the updated TOUS (Lenz et al., 1997), the direction of the interaction is inconsequential because caregiver burden and agitation are constantly interacting and creating feedback within each other.

Findings from the path analysis were further supported with exploratory data from subsets of participants. Correlations between a specific measure of situation (the Zarit Burden Interview and NPI occupational disruption scale) and measures of agitation (the CMAI and NPI agitation subscale) were found. A nearly perfect correlation was found between the ZBI and CMAI for the 5 participants with both measures, and the NPI occupational disruptiveness scale was moderately correlated with both CMAI and NPI agitation.

Psychological states. The final path model showed strong support for the relationships between psychological symptoms and agitation. It was previously demonstrated that psychological disturbances often co-occur with agitated behavioral symptoms in persons with AD (Borsje et al., 2015; Chen et al., 2014; Van der Mussele et al., 2015). This research further

confirms co-occurrences of psychological disturbances and agitation, and suggests that states of psychological distress may exacerbate agitated behavioral symptoms in persons with AD.

In addition to the evidence supporting the relationship between increased psychological disturbances and agitation discovered through the path analysis, additional exploratory evidence further supports these findings. The ADAS non-cognitive behavioral scale was correlated with the FAC agitation scale. While not measured in the path analysis, this provides further evidence supporting the relationship between agitation and other neuropsychiatric symptoms in AD across different instruments of measurement.

Physical Health. The path analysis found a strong relationship between the cognitive aspect of physical health and agitated behavioral symptoms. This relationship is consistent with previously reported findings of increasing agitation with diminishing cognition (Chen et al., 2014; Livingston et al., 2017; Ryu et al., 2005; Veldwijk-Rouwenhourst et al., 2017). Contradictory evidence was reported by Lovheim et al., (2008) who reported that agitation increased with cognitive decline only to the point of moderate dementia impairment, and then subsided. Disagreements in previous reports of the relationship between agitated behavioral symptoms and cognitive measures may be attributable to definition of dementia with agitation being more prevalent in dementia related to AD than other types of dementia (Apostlova et al., 2014; Steinberg et al., 2006).

Although other measures of physical comorbidities were not measured in the path analysis, exploratory evidence suggested the existence of correlations between pain and agitation. The relationship between pain and agitation has been demonstrated in many previous studies (Pelletier & Landreville, 2007; Volicer et al., 2012). Volicer and colleagues (2012) only found a relationship between agitation and pain when dementia severity and functional disability

were controlled, and Chen (2014) found an indirect relationship between pain and agitation through the effect of pain on depression and functional disability suggesting that the relationship between agitation and pain is sometimes complex. Findings that the treatment of pain reduces agitated behaviors suggest that agitated behavioral symptoms can be a response to untreated pain (Husebo, Ballard, Cohen-Mansfield, Seifert, & Aarsland, 2014). The modifiable relationship between pain and agitation demonstrates the need to assess and treat pain in persons with AD.

Surprisingly, exploratory evidence did not identify relationships between cumulative disease burden (CIRS-G), nutritional measures (MNA, NPI Appetite), or hearing (HHIE-S) and agitation. Sample sizes for these exploratory comparisons were small ($n = 5-18$), which may have contributed to the lack of observed relationships. Although correlations cannot determine cause and effect relationships, these are interesting findings that could be explored further in future analyses.

Agitation. Agitation was measured with three different tools concurrently: CMAI, FAC agitation subscale, and NPI agitation subscale. Surprisingly, these measures demonstrated minimal intercorrelation among measures (only CMAI and FAC agitation subscale were significantly correlated). There were, however, strong correlations between CMAI and NPI disinhibition, aberrant motor behavior, and irritability subscales, between the FAC agitation subscale and the ADAS non-cognitive behavioral subscale, and also between the NPI agitation subscale and NPI aberrant motor behavior and NPI irritability subscales.

This clearly demonstrates the inconsistencies with which AD-related agitation is described by different authors and is measured by different tools. With the broadest definition of agitation, Cohen-Mansfield and Billing (1986) consider verbal aggression, physical aggressive and non-aggressive behaviors, as well as hoarding to all measure different aspects of the broader

construct of agitation. This overlaps with related concepts that others describe as restlessness, aggression, aberrant motor behaviors, or inappropriate behaviors (Cummings et al., 2015, Kong, 2005). While some researchers narrow the conceptual definition of agitation to exclude related factors, others measure agitation broadly and may simply explain the broad construct as “agitation and aggression” (de Mauleon et al., 2019). This broad approach seems to be the most effective since the reported consequences of agitation-related challenging behavioral symptoms in AD are similar, including increased caregiver burden and institutionalization (de Mauleon et al., 2019; Dufournet et al., 2019). No evidence was found to support different patient outcomes for different types of agitation, but if future evidence suggests that different types of agitation do impact different outcomes, then the narrow definition of agitation would be appropriate.

Functional Outcomes. In the present study, functional outcomes were conceptualized both as functional abilities and quality of life. Only measures of functional ability were measured in the path analysis due to sample size constraints. The model found no support for the effects of situational and psychological predictors on functional performance or the relationship between agitated behavioral symptoms and functional outcome. This may be attributable to caregiver perceptions of functional deficits as less burdensome than other AD-related symptoms (Dufournet et al., 2019). Many caregivers report less psychological burden from physical and cognitive AD-related deficits than from agitation. However, these three factors are directly tied to over 84% of nursing home admissions for persons with AD and all merit in-depth exploration (de Mauleon, 2019; Dufournet et al., 2019).

A relationship between physical predictors and functional outcome was supported by the path model. The spurious relationship calculated between agitation, functional outcome, and physical factors indicated that agitation and functional outcomes were both the result of physical

factors as opposed to a direct relationship between agitation and functional outcome. This is consistent with the disease course of AD causing both functional and cognitive decline and worsening neuropsychiatric symptoms as neuropathological changes worsen (Braak & Braak, 1991; Tward et al., 2017; Maas et al., 2015; Serrano-Pozo et al, 2011; Tam & Pasternak, 2017). No other factors measured in this analysis contributed any noticeable effect on this relationship.

Exploratory evidence based on small samples indicated that caregivers felt more burdened when individuals with AD had later-staged illness (ZBI was correlated with GDS/FAST stage, $n = 5$), and that burdened caregivers rated lower quality of life for individuals with AD (ZBI was correlated with ADRQL, $n = 5$). Previous findings have also indicated that caregiver-reported quality of life for individuals with dementia diminished as the disease progresses, and that these changes are often accompanied by increasing levels of agitation (Livingston et al., 2017). Quality of life is an important outcome that should be measured in additional research.

Functional performance outcomes and psychological factors were not found to be related in the path analysis, and no additional significant findings were uncovered through individual analyses. There were no participants with concurrent measures of quality of life and psychological indicators, so no conclusions can be drawn.

Exploratory evidence was found to support the relationship between increased comorbid disease burden and worsening function status as well as quality of life (CIRS-G correlations to FAC self-care, $n = 13$; GDS/FAST scores, $n = 5$; and ADRQL, $n = 5$). Other authors examining quality of life from the perception of both caregivers and patients have also found lower quality of life and functional status in individuals with high comorbid disease burden in AD, and

attributed lower quality of life ratings to issues pertaining to dignity, disease development, health and function, and safety issues (Verloo, Salina, Fiorentino, & Cohen, 2018).

Further initial evidence suggests a correlation between worsening nutritional status and lower quality of life, although the sample was small (MNA was correlated with QOL-AD, $n = 5$). These findings are consistent with previous research that nutrition, weight, and quality of life declined over a one-year study of persons with AD (Suominen et al., 2015). Suominen and colleagues (2015) also reported that tailored nutritional interventions resulted in little change in quality of life and no change in nutritional status. As reduced oral intake is an expected outcome of advanced-stage AD, it is important to evaluate the stage of AD when considering aggressive dietary interventions (Ferrell, Twaddle, Melnick, & Meier, 2018). Avoidance of forced feeding can be part of compassionate end of life care (Post, 2001).

Limitations

Limitations of methods

This dissertation was a secondary analysis of cross-sectional, descriptive data from multiple parent studies. Cross-sectional studies are limited by their snapshot perspective on study variables. In contrast, longitudinal studies are particularly important to studying degenerative diseases like AD by examining the declining trajectory over time rather than instantaneous observations. Individual variations between baseline features can complicate the separation of signal from noise in the analysis of differences. To help clarify differences between individuals which are attributable to AD-related decline and differences between individuals at baseline, longitudinal measurements are the gold standard for all aspects of AD research from neuroimaging, to biomarkers to cognition (Jack et al., 2014; Raz & Kennedy, 2009; Xu et al., 2014).

Original parent studies employed a convenience sample for enrollment of participants. Eligible participants and their caregivers voluntarily enrolled in the study without random selection. Without random sampling, there may have been systematic error introduced to the data due to unmeasured similarities between participants which limits the ability of results to be generalized.

Secondary analysis provides unique limitations as well as benefits compared to original research. In secondary analysis, the researcher is committed to measuring study variables with the instruments that have already been used. Therefore, careful evaluation of psychometric properties was necessary. It was also important to assure that research questions could be adequately addressed by the existing data set. Benefits of secondary analysis include accessing larger pools of participants than would otherwise be possible and that secondary analysis can be used to answer new research questions without further burdening vulnerable populations (Wickham, 2019). Despite its limitations, secondary analysis is a useful and appropriate method for answering the observational and theory-based research questions examined in this research study.

Limitations of results

There are limits to generalization of these research findings to wider populations. The individuals in this sample were mostly females and almost entirely white. Male gender is has previously been associated with agitation and aggression in AD (Kolanowski, 2016). Conversely, female gender has been associated with higher levels of psychosis (delusions and hallucinations) in AD (Nagata et al., 2017). It has been suggested that caregiver burden experienced by female family members caring for agitated males with AD may be related to traditional gender roles causing some females to perceive helplessness or inappropriateness in

controlling these challenging behaviors (Tan et al., 2005). It is unclear if females who suffer from AD have a different presentation, experience, or consequences to agitated behavioral symptoms or if their symptoms are interpreted differently than males. The lack of individuals from non-white backgrounds in this sample presents a barrier to wide generalization of these results as individuals with racial or ethnic minority backgrounds may have unique socioeconomic circumstances, physical comorbidities, or social environments impacting agitation.

Traditionally, symptoms are characterized as subjective experiences known only to the individual, whereas signs are observable by others (MacBryde & Blacklow, 1983). In AD, diminishing mental ability caused by the disease interferes with an individual's ability to recognize and express their symptom experience. For this reason, AD symptoms are usually considered to include any manifestation of AD as observed by individuals or their caregivers (Hutchinson & Wilson, 1998). It is not known how accurately these observable signs represent the internal symptom experience of individuals (Lenz & Gift, 1998). The extent to which signs are recognized by outside observers presents a barrier to understanding the true symptom experience in this population.

Although many of the hypothesized relationships surrounding the symptom experience of agitation were supported through the analysis of the data, agitation and other background factors did not demonstrate the expected relationships with functional performance outcomes and quality of life measures. Many potentially important variables like stability of place of residence, family support, social isolation, hearing loss, comorbid disease burden, pain, and quality of life were not measured in the model. These factors could affect the results.

There is still not enough evidence to definitively determine a comprehensive list of antecedents and consequences to agitation, and more evidence is needed to decide for certain if the TOUS is the best model for understanding this phenomenon. The original version of the TOUS provided a simple and straightforward model from which the symptom experience could be understood. The updated version of the TOUS introduced more complexity. It may provide a better understanding of the symptom experience from a longer term view, but also created a less specific, recursive model of the symptoms where every variable essentially impacts every other variable concurrently. This type of relationship does not lend itself well for cross sectional analysis, and so little support for the updated TOUS can be determined by the present analysis.

Although limitations in this research are acknowledged, the results do contribute to a wider body of knowledge to improve the care of individuals with AD and their family members. Importantly, it demonstrates a unique application of the Nursing TOUS to guide a model of agitated behavioral symptoms in individuals with AD. From this theory-guided model, predictors of agitated behavioral symptoms were identified, and limitations to the application of TOUS in persons with AD were suggested.

Recommendations for Future Research

This study has partially validated the utility of the TOUS in describing and predicting agitated behavioral symptoms in persons with AD. Further research into other possible antecedents to agitated behavioral symptoms as well as consequences of agitation are necessary to provide further guidance to the utility of the TOUS in the population, and to identify opportunities for interventions to improve life individuals with AD and for caregivers.

Theory testing

More testing of the TOUS is necessary to determine its utility in understanding behavioral symptoms in persons with Alzheimer Disease. The qualitative research by Hutchinson & Wilson provides an excellent example of how the TOUS can be applied to systematically understanding the symptoms of AD through real-world episodic cases. Rather than asking participants about experiences from the prior week or month, specific instances of problematic behaviors were examined within the TOUS framework. From these examples, antecedents can be identified to reduce future recurrences of the problematic symptoms or performance outcomes. The same approach could be applied to the development of an intervention support caregivers in managing episodes of agitated behaviors. Because the application of the TOUS to populations with AD has been mixed, future studies should also compare results to other available nursing theories like the NDB (Algase et al., 1996), unmet needs framework (Cohen-Mansfield, 2000), and PLST (Hall & Buckwalter, 1987) models of behavior in AD.

The TOUS should be tested over longer time frames to determine if the updates made in the second version of the TOUS mitigate some of the deficiencies in the original version. French, Crawford, Bova, and Irwin (2017) found that many of the antecedent factors identified in their understanding of chronic cough were improved by managing the symptoms itself, supporting the hypothesized feedback loop proposed in the updated model of the TOUS. A similar analysis could be examined within the phenomenon of agitated behavioral symptoms in AD through an analysis of data collected at multiple time points.

Antecedents

Other environmental factors (such as the physical surroundings, changes to daily routines, level of stimulation, noise, social engagement) have previously demonstrated a relationship with agitated behavioral symptoms (Corcoran & Gitlin, 1992; Kolanowski et al., 2017; Livingston et al., 2014; Ragneskog et al., 1998; Smith et al., 2006). These specific environmental variables were not tested within the situational theoretical construct of the TOUS in the current study. Testing the effects of these factors on agitated behavioral symptoms and functional performance outcomes would add evidence to the extent and importance of environmental variables that may impact outcomes within the TOUS, and also potentially provide evidence for interventions to improve these outcomes.

Because depression and anxiety are themselves symptoms of Alzheimer disease, future studies could consider premorbid psychiatric illness rather than only comorbid psychiatric states. This follows the method suggested by Kolanowski and colleagues (2017). This method could further elucidate the independent effects of premorbid psychiatric concerns rather than neuropsychiatric symptoms that occur as a direct result of the course of AD symptoms.

This research found that the role of caregiver burden is very important in explaining agitated behavioral symptoms. As this is one of the few modifiable antecedents of agitated behavioral symptoms in AD, this area should be prioritized for future intervention research. In an initial trial of a comprehensive dementia care program, Rueben and colleagues (2019) found that individualized dementia care plans, dementia management skills training, and caregiver support groups helped improve neuropsychiatric symptoms and caregiver burden after one year, although functional ability continued to decline. Programs like this should be optimized through

continued research and targeted to improve support for caregivers throughout the disease progression. Similar programs should be tested to determine efficacy for professional caregivers.

Finally, future research should focus on diverse populations and include participants from racial and ethnic minority backgrounds. Interpreted within the TOUS, racial or ethnic experiences could potentially contribute to differential expressions of agitation through physical or situational antecedent risks. Physical risks such as cardiovascular disease and other comorbid health conditions are more prevalent African American and Hispanic populations (Chin, Negash, & Hamilton, 2011). Social risks for minority populations are extensive and may include environment, educational background, stigmatization, and access to care (Dilworth-Anderson, Pierre, & Hilliard, 2012; Weuve et al., 2017). More research is necessary to validate the degree to which the TOUS adequately describes the impact of these risk factors on agitated behavioral symptoms in AD. Future research should focus on modifiable risk factors to target future interventions.

Agitation

Greater conceptual clarity is still a major concern in defining and describing this phenomenon. Although some work to clarify the concept has been made through efforts such as the Agitation Definition Work Group of the International Psychogeriatric Association, its definition of agitation has not been fully translated into research as evidenced by the continued use of tools that operationalize agitation narrowly. This research emphasizes the close association of agitation and related concepts like irritability or aberrant motor behaviors. Future research may consider combining closely related concepts into a single “agitation/aggression” factor (de Mauleon et al., 2019). This is especially important with the recognition that different individuals may have different expressions of “behaviors consistent with emotional distress”

(Cummings et al., 2015, p. 7). To definitively end the disagreements over which behaviors should and should not be included in the conceptualization of agitation, research into specific components of agitation should seek to understand if these behaviors occur independently of one another, and if their causes or consequences are different. If no differences are found, then the broad definition of agitation and related behaviors should prevail.

Functional outcomes

Quality of life measures are of utmost importance in evaluating care decisions made on behalf of older adults with AD. While treatment for AD remains elusive, AD is a terminal illness. As such, principles of palliative care, such as maximization of comfort and quality of life, are paramount outcomes in caring for this population (Volicer & Simard, 2015). Although these outcomes were not fully investigated in the present study, they warrant thorough research in the future.

Implications for Nursing Practice

Agitation is a common but distressing behavioral symptom in persons with AD. Agitation is unpleasant for both individuals as well as their professional and family caregivers (Chiao et al., 2015, Hongisto et al., 2015, Tan et al., 2005). The model of agitated behavioral symptoms in AD described in this research is useful for nursing practice in the assessment of patient needs, planning for long term care needs, and implementing nursing interventions.

Persons with AD are often unable to fully communicate their needs, especially as the disease progresses. For this reason, it is especially important for nurses to assess any possible physical, psychological or situational cause of agitation. This research suggests that untreated pain may be expressed as agitation, and should be carefully assessed. Psychological states may be resultant of the AD process (Borsje et al., 2015; Chen et al., 2014; Van der Mussele et al.,

2015), but should also be assessed as possible contributing factors to expressions of agitation (de Mauleon et al., 2019).

As AD is a long-lasting illness, long-term needs should be assessed and discussed with caregivers. When individuals with AD are cared for in the home, their situation should be monitored and needs for additional services should be frequently reassessed as their situation changes over time (Reuben et al., 2019). Although the impact of agitation and its antecedents on quality of life was not fully investigated in this study, it remains an important outcome as identified in the TOUS. While planning the for the long-term care needs of individuals with AD, end of life plans should be discussed at the earliest opportunity to assure that quality of life remains a priority in all care planning decisions (Ferrell et al., 2018).

This model, as well as previous evidence, has clearly demonstrated the close relationship between caregiver distress and agitated behavioral symptoms in AD (de Mauleon et al., 2019). Nursing interventions to prevent or relieve the distress in both professional and family caregivers are necessary for the wellbeing of the caregivers as well as a means of improving the agitated behavioral symptoms directly. Interventions that have demonstrated improvements in the caregiver experience include respite care for family members, communication training, and support groups (Barbosa, Nolan, Sousa, & Figueiredo, 2015; Reuben et al., 2019). These interventions should be implemented for both professional and informal caregivers of persons with AD.

Conclusion

As the United States and much of the world consider ways to confront the impending surge of older adults who are likely to require care for AD and its related symptoms, research into mitigating the most challenging symptoms of this devastating disease are critically

important. This research found that the TOUS can provide a valid and important conceptual map for understanding, predicting, and potentially controlling agitated behavioral symptoms in older adults with AD. Until treatment or prevention of AD is possible, more work is necessary to minimize symptoms and maximize functional performance to enable older adults with AD and those who provide care to live with the most independence and dignity as possible. This research supports the use of the TOUS as a framework to guide this effort, and provides evidence of the TOUS's pragmatic utility in nursing research and practice.

APPENDIX A

IRB Exemption

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87 East Canfield, Second Floor
Detroit, Michigan 48201
Phone: (313) 577-1628
FAX: (313) 993-7122
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CONCURRENCE OF EXEMPTION

To: Katherine Kero
Deans Office Nursing

For
From: Dr. Deborah Ellis M. Tancer, MD / BC
Chairperson, Behavioral Institutional Review Board (B3)

Date: October 11, 2018

RE: IRB #: 094618B3X

Protocol Title: A MODEL OF AGITATED BEHAVIORAL SYMPTOMS IN PERSONS WITH ALZHEIMER DISEASE

Sponsor:

Protocol #: 1809001766

The above-referenced protocol has been reviewed and found to qualify for **Exemption** according to paragraph #4 of the Department of Health and Human Services Code of Federal Regulations [45 CFR 46.101(b)].

- Social/Behavioral/Education Exempt Protocol Summary Form (received in IRB Office 10/10/2018)
- Research Protocol (received in the IRB Office 10/10/2018)
- Medical records are not being accessed therefore HIPAA does not apply
- Theoretical Term Study Tool

This proposal has not been evaluated for scientific merit, except to weigh the risk to the human subjects in relation to the potential benefits.

-
- Exempt protocols do not require annual review by the IRB.
 - All changes or amendments to the above-referenced protocol require review and approval by the IRB **BEFORE** implementation.
 - Adverse Reactions/Unexpected Events (AR/UE) must be submitted on the appropriate form within the timeframe specified in the IRB Administration Office Policy (<http://irb.wayne.edu/policies-human-research.php>).

NOTE: Forms should be downloaded from the IRB Administration Office website <http://irb.wayne.edu> at each use.

Notify the IRB of any changes to the funding status of the above-referenced protocol.

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ABSTRACT**A MODEL OF AGITATED BEHAVIORAL SYMPTOMS IN PERSONS WITH ALZHEIMER DISEASE**

by

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Background: Worldwide population trends are shifting with the population of Elders expected to dramatically increase in absolute and relative numbers in coming years. Alzheimer Disease (AD) is a common and costly disease of aging with agitation being the most poorly managed and detrimental behavioral symptom of the condition. The Nursing Theory of Unpleasant Symptoms provides a conceptual basis for understanding agitated behavioral symptoms associated with AD in the context of its antecedent causes and outcomes of the symptoms.

Purpose: The purpose of this dissertation was to model the predictors and outcomes of agitated behavioral symptoms in persons with AD. The specific aims were: (1) Describe the phenomenon of agitated behavioral symptoms in persons with AD within the Theory of Unpleasant Symptoms; (2) Determine the effect of situational, psychological, and physiological factors on agitation in persons with AD; (3) Determine the effect of situational, psychological, and physical antecedent factors and agitation on performance outcomes.

Methods: A descriptive, correlational, cross-sectional, secondary analysis research design will be employed. The original data were collected in communities and in Nursing Homes settings in the Midwestern US. A convenience sampling of facilities yielded 120 participants.

Results: Exploratory factor analysis identified three antecedent factors to agitated behavioral symptoms: Situation-Caregiver, Psychological, and Physical-Cognitive. The path analysis model closely represented all variables and relationships predicted in the TOUS ($\chi^2 = 1.049$, $df = 2$, $p = .592$). Significant relationships between situation and agitation ($B = 0.51$, $p < .001$), psychological symptoms and agitation ($B = 0.446$, $p < .001$), and physical health on agitated behavioral symptoms ($B = 0.58$, $p = .001$) were found, and explained 63% of the variance in agitation. The model found no support for the effects of any measured factors on performance outcomes, except the effects of the Physical: Cognitive factor ($B = 0.86$, $p < .001$) which explained 66% of the variance in functional performance.

Implications: The TOUS provides a good model to identify causes of agitated behaviors in AD. This study emphasizes the need for greater support of caregivers of persons with AD because caregiver burden is an important modifiable antecedent to agitated behavioral symptoms. Future research should investigate interventions to reduce professional and informal caregiver burnout and study the effects of reduced caregiver burnout on improvements in agitated behavioral symptoms in persons with AD. Future research should also evaluate quality of life outcomes to better determine if the relationships between symptoms and performance outcomes predicted in the TOUS remain valid in persons with AD.

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