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**PERSONALITY AS A MODERATOR OF COGNITIVE STIMULATION
OUTCOMES IN OLDER ADULTS AT HIGH RISK FOR COGNITIVE DECLINE**

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Nikki L. Hill

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The dissertation of Nikki L. Hill was reviewed and approved* by the following:

Ann M. Kolanowski
Professor of Nursing
Dissertation Advisor
Chair of Committee

Donna M. Fick
Distinguished Professor of Nursing

Vernon Chinchilli
Distinguished Professor of Statistics

Rita Jablonski
Associate Professor of Nursing

Judith E. Hupcey
Professor of Nursing
Associate Dean for Graduate Education

*Signatures are on file in the Graduate School.

Abstract

Background: Individuals with dementia and delirium experience an accelerated period of cognitive decline which is often unresolved, leading to long-term negative consequences. Interventions targeting acute cognitive decline in this population are largely unexplored, and moderators of intervention effectiveness have yet to be determined.

Purpose: The purpose of this study was to determine whether personality moderated cognition-focused intervention outcomes in individuals at high risk for cognitive decline: those with dementia and delirium.

Methods: This study utilized a portion (n=71) of the sample participating in a randomized repeated measures clinical trial, Recreational Stimulation for Elders as a Vehicle to Resolve Delirium Superimposed on Dementia (RESERVE-DSD). Subjects with dementia and concurrent delirium were recruited upon admission to one of seven Pennsylvania nursing homes with post-acute services for rehabilitation following hospitalization; all diagnoses were adjudicated by an expert panel. The control group received routine nursing care and prescribed therapies as typically delivered for their particular health condition. In addition to usual care, subjects randomized to the treatment group received 30 minutes of cognitive stimulation daily for up to 30 days. The intervention consisted of personally tailored, mentally challenging recreational activities that incrementally increased in difficulty. Baseline measures included demographic characteristics, ApoE ϵ 4 status, Lifetime of Experiences Questionnaire, the Modified Blessed Dementia Rating Scale, and the NEO™ Personality Inventory-3. Measures of delirium, attention, orientation, memory, and executive function were taken daily for both groups. Engagement in the intervention was measured by the time spent on task (up to 30 minutes) as well as the level of participation. Linear mixed-effects models were used to examine the moderating effects of the five personality traits on the four cognitive outcomes, as well as main effects on engagement outcomes among the treatment group.

Results: Significant moderating effects of personality traits were found with regard to two cognitive outcomes: agreeableness moderated the memory outcome and extraversion moderated the executive function outcome. Individuals with higher agreeableness were more likely to have improved memory outcomes, and those with lower extraversion more likely to have improved executive function outcomes, as a result of the cognition-focused intervention. Lower openness, higher agreeableness, and lower conscientiousness were associated with greater engagement in the intervention.

Conclusion: Personality traits are known to influence a wide variety of health and treatment outcomes, and their role in cognition-focused interventions for individuals with dementia and delirium is in line with these findings. The consideration of personality in further development and testing of these interventions will provide for clarification and characterization of these effects.

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Chapter 1

Introduction

Many older adults, an estimated 14.7% of those age 70 or older in the United States, are at risk for debilitating cognitive decline due to Alzheimer's disease (AD) and other dementias (Hurd, Martorell, Delavande, Mullen, & Langa, 2013). Dementia due to AD was estimated to affect 4.7 million older adults in 2010, and is expected to increase to 13.8 million in 2050 with the growth of the aging population (Hebert, Weuve, Scherr, & Evans, 2013). In addition to the devastating effects for those diagnosed as well as their loved ones, the total annual societal cost of dementia in 2010 was estimated to be between \$125 and \$157 billion, more than heart disease or cancer (Hurd, et al., 2013).

Individuals with dementia are highly susceptible to an acute decline in cognitive functioning, or delirium, when faced with a stressor such as illness or hospitalization (Fick, Agostini, & Inouye, 2002). Delirium in this already vulnerable population is associated with significant negative consequences including a hastened dementia trajectory (Fick, et al., 2002; Gross, et al., 2012), increased morbidity and mortality (Kiely, et al., 2009; Voyer, Cole, McCusker, & Belzile, 2006), as well as increased healthcare costs (Leslie, Marcantonio, Zhang, Leo-Summers, & Inouye, 2008). Medications are generally contraindicated in the treatment of delirium (Fong, Tulebaev, & Inouye, 2009), but very few studies have tested non-pharmacological approaches in this particularly vulnerable population (Fick, et al., 2002). No studies have examined individual participant characteristics which may contribute to intervention success.

This study investigated personality as a moderator of cognition-focused treatment outcomes among older adults at high risk for accelerated cognitive decline. It was conducted concurrently with a randomized controlled trial (RCT) of cognitively stimulating activities, Recreational Stimulation for Elders as a Vehicle to resolve DSD (RESERVE-DSD; Kolanowski, Litaker, Clare, Leslie, & Boustani, 2011), utilized a portion of the study's sample, and included an additional assessment of premorbid personality, or

personality prior to the onset of cognitive impairment. This study tested the moderating effects of five personality traits on cognitive function as well as the effects of personality on engagement in the intervention, among individuals with dementia experiencing delirium.

Statement of the Problem

Two conditions responsible for debilitating cognitive decline in older adults are dementia and delirium. Individuals with dementia who develop delirium experience an accelerated period of cognitive decline which is often unresolved, leading to long-term negative consequences. Interventions targeting acute cognitive decline in this vulnerable population are largely unexplored, and moderators of intervention effectiveness have yet to be determined.

Characterization of Dementia and Delirium

Alzheimer's disease is the most common cause of dementia, although it is now recognized that up to half of all cases of AD demonstrate mixed pathologies on autopsy such as vascular components (Aguero-Torres, Kivipelto, & von Strauss, 2006; Armstrong, Lantos, & Cairns, 2005; Schneider, Arvanitakis, Leurgans, & Bennett, 2009). Dementia symptoms are persistent, worsen over time, and include impairments in language, memory, visuospatial skills, and intellectual abilities that are severe enough to interfere significantly with daily life (American Psychiatric Association, 2000; Cummings & Mega, 2003). The progressive cognitive decline associated with dementia is devastating for those diagnosed as well as their 15.4 million informal caregivers (Alzheimer's Association, 2013). At present, no treatment is available to reverse the progression of dementia, but rehabilitation to optimize cognitive functioning is a realistic goal (B. Wilson, 2008).

Delirium is an acute clinical syndrome characterized by fluctuating level of consciousness and pervasive impairment in mental, behavioral, and emotional functioning (American Psychiatric Association, 2000). In contrast to dementia, it is transient and potentially reversible, although it can become chronic and cause permanent disability if untreated (Fong, Tulebaev, et al., 2009). Delirium is

associated with a downward spiral of events leading to loss of independence, decreased functional ability, declines in health status, and death (Inouye, 1998, 2006; Kiely, et al., 2009).

Individuals with dementia are particularly susceptible to delirium development upon exposure to a precipitating stressor (Inouye, 1999; Young, Murthy, Westby, Akunne, & O'Mahony, 2010). The highest rates of delirium are in hospitalized older adults with dementia; prevalence rates range from 32% to 89% (Fick, et al., 2002; Gross, et al., 2012). These acute cognitive changes frequently remain unresolved prior to discharge. Among individuals admitted to post-acute care facilities following hospitalization, an average of 1 in 7 met criteria for delirium with rates ranging from 1 in 4 to 1 in 15 across facilities (Jones, Kiely, & Marcantonio, 2010). Therefore, the persistence of delirium among individuals with dementia following hospitalization is relatively common.

Dementia's Negative Consequences Compounded by Delirium

Individuals with dementia are inherently vulnerable to cognitive decline as a result of AD and other pathology, and those who also develop delirium are furthermore highly susceptible to an accelerated trajectory of decline (Gross, et al., 2012; Kolanowski, Fick, Clare, Therrien, & Gill, 2010; Voyer, Richard, Doucet, Danjou, & Carmichael, 2008). Delirium in individuals with dementia is associated with hastened dementia progression, prolonged hospitalization, re-hospitalization, institutionalization (Fick, et al., 2002), as well as twice the mortality risk after discharge compared to those with dementia or delirium alone (Bellelli, et al., 2007).

In addition to the negative impact on the individual, societal costs are significant. Hospitalized patients with delirium are over two times more expensive to care for than patients without delirium; delirium-specific costs range from approximately \$16,000 to \$64,000 per patient over a period of one year (Leslie, et al., 2008). Total annual U.S. healthcare costs attributed to delirium are estimated to be between \$143 and \$152 billion (Leslie & Inouye, 2011). Therefore, the ability to restore cognitive

functioning to baseline levels by timely resolution of the acute cognitive decline of delirium benefits the individual with dementia and the healthcare system overall.

Need for Interventions to Resolve Delirium in Persons with Dementia

Although the onset of delirium in individuals with dementia often heralds the beginning of an accelerated downward spiral of negative consequences, very few studies have tested non-pharmacological treatments to restore baseline cognitive functioning (Cole, 1999; Fick, et al., 2002). Delirium interventions in older adults have targeted prevention rather than resolution of an incident delirium (Milisen, Lemiengre, Braes, & Foreman, 2005; Miller, 2008; Weber, Coverdale, & Kunik, 2004) or have been largely unsuccessful, even when geriatric professionals are included in the program (Weber, et al., 2004). These multi-component interventions also limit the ability to determine individual aspects of the program that may be effective since it is often difficult to identify the unique contribution of each component.

Since the potential for adverse reactions to medications in older adults is high, the development of well-targeted, non-pharmacological treatments for those at high risk for accelerated cognitive decline is urgently needed (Fong, Tulebaev, et al., 2009). Studies exploring effective management of delirium in individuals with dementia have been identified as a critical component of future research (Fick, Kolanowski, Beattie, & McCrow, 2009; Kolanowski, Fick, Clare, Therrien, et al., 2010). A pilot study of cognitively stimulating activities for individuals with dementia experiencing acute cognitive decline in a post-acute setting demonstrated feasibility as well as preliminary evidence of cognitive benefit (Kolanowski, Fick, Clare, Steis, et al., 2010).

Although there is a dearth of non-pharmacological treatments for acute cognitive decline investigated in the scientific literature, a variety of interventions have been tested for their ability to improve cognitive functioning in persons with dementia. As a group, these approaches are referred to as cognition-focused interventions and they utilize multiple strategies in order to improve cognitive

function (Aguirre, et al., 2010; Clare, 2010). Cognition-focused treatment targeting the domains most affected by delirium, including attention, orientation, memory, and executive function, may improve cognitive functioning to the point of restoring the individual with dementia to his or her baseline functional level, thus avoiding life-altering and costly consequences.

Proposed Mechanisms of Cognition-Focused Interventions for Cognitive Decline

Due to the multiple interconnections between dementia and delirium, it has been proposed that they may represent aspects of the same underlying condition (Fick, et al., 2009; Hshieh, Fong, Marcantonio, & Inouye, 2008; Inouye & Ferrucci, 2006; Murray, et al., 1993). Even individuals with pronounced brain vulnerability, such as those with mild to moderate dementia, have demonstrated improvements in cognition after a cognition-focused intervention (Aguirre, Woods, Spector, & Orrell, 2013) as well as the ability to learn and employ cognitive strategies (Clare, et al., 2010). Intervention approaches that demonstrate effectiveness in individuals with dementia may also be effective in addressing acute cognitive decline in this population.

Cognition-focused interventions are thought to mediate improvement in cognitive function by stimulating brain plasticity, or the ability of the brain to remodel neural pathways in order to optimize function (Duffau, 2006). The brain retains an ability to expand and establish connections when exposed to mentally stimulating activities throughout old age (Vance, et al., 2008), perhaps as a compensatory mechanism (Meade & Park, 2009). Improvement in cognitive function is thought to be possible due to retained plasticity mechanisms, including among individuals with heightened vulnerability to cognitive decline such as those with dementia (N. L. Hill, Kolanowski, & Gill, 2011).

Inducing plasticity via mental stimulation is thought to not only improve immediate processing, but also reduce brain vulnerability by increasing cognitive reserve (Le Carret, et al., 2005; Newson & Kemps, 2006). The concept of cognitive reserve derived from the observation that individuals with the same level of dementia-related pathology may vary considerably in clinical presentation and progression

(Katzman, et al., 1988; Stern, 2002). Cognitive reserve is hypothesized as the ability of the brain to withstand a certain level of injury before the clinical manifestation of cognitive deficits. This ability varies between individuals based on innate protective effects as well as ability to utilize compensatory mechanisms (Stern, 2006, 2012). Brain plasticity is thought to contribute significantly to the ability to build cognitive reserve (Bach-y-Rita, 2003). Targeting brain plasticity in a cognition-focused intervention has the potential to build cognitive reserve and therefore reduce the impact of factors contributing to cognitive decline in individuals with dementia and delirium.

Identifying Moderators of Cognition-Focused Interventions

While few non-pharmacological treatments for acute cognitive decline have been investigated in the scientific literature, cognition-focused intervention programs such as cognitive stimulation have demonstrated success in improving cognitive abilities in individuals with dementia (Aguirre, et al., 2013; Clare, et al., 2010; Woods, Aguirre, Spector, & Orrell, 2012). However, synthesis of the evidence regarding cognition-focused approaches across the larger body of literature indicates mixed results, with some studies demonstrating cognitive function benefits (Aguirre, et al., 2013; Woods, et al., 2012) and others demonstrating no change (Papp, Walsh, & Snyder, 2009). A potential contributor to these results that has not yet been considered is the moderating effect of personal characteristics on cognition-focused intervention outcomes; it is not known whether some individuals are better candidates due to characteristics such as personality or preferences.

It is well-accepted in experimental research that an effective intervention may not be equally effective among individuals. Moderators of intervention outcomes characterize individuals more likely to respond to treatment and help identify best candidates for that particular treatment (Kraemer, Kiernan, Essex, & Kupfer, 2008). It has been suggested that RCTs include secondary exploratory moderating analyses in order to inform future research design (Kraemer, Frank, & Kupfer, 2006). Furthermore, it has been recommended that nurse scientists consider the effects of moderators in order

to gain additional information regarding the circumstances under which a nursing intervention provides the best outcome (J. A. Bennett, 2000).

Personality as a Moderator of a Cognition-Focused Intervention

Personality, or an individual's relatively stable intrinsic structure of thinking, feeling, and behaving (Roberts & Mroczek, 2008), may contribute to outcomes of cognition-focused interventions. The predominant framework in scientific research describing the structure of personality is the five-factor model, which consists of five broad personality traits: *neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness* (Costa, 1991). Personality's influence on health outcomes such as participation in and benefit from behavioral interventions in other populations is well-established (e.g., Bogg & Roberts, 2004; Conner, Rodgers, & Murray, 2007; de Bruijn, Brug, & Van Lenthe, 2009; Judge & Ilies, 2002). Multiple studies have demonstrated the moderating effect of personality on health and treatment effects (Franks, Chapman, Duberstein, & Jerant, 2009; Rossi, Bisconti, & Bergeman, 2007), its association with chronic disease outcomes (Paika, et al., 2010), as well as its relationship to motivation, performance, and treatment adherence (Hooten, 2005; Hurtz & Donovan, 2000; Judge & Ilies, 2002). Personality can guide therapeutic activity interventions for individuals with dementia leading to increased engagement in those activities and resultant reduced passivity (N. L. Hill, Kolanowski, & Kurum, 2010; Kolanowski & Buettner, 2008; Kolanowski, Litaker, & Buettner, 2005; Kolanowski, Litaker, Buettner, Moeller, & Costa, 2011). The potential of personality to effectively guide dementia intervention development is established; however, the influence of personality traits on cognition-focused intervention effectiveness in persons with dementia and delirium has not been examined.

Summary: Statement of the Problem

Dementia is a devastating syndrome with multiple causes, most commonly including AD pathology. In addition to the cognitive deficits associated with dementia, afflicted individuals are

susceptible to acute declines in cognition following a stressor such as hospitalization. These declines, referred to as delirium, often lead to long-term negative consequences if not resolved. Effective interventions have not been established to return individuals with dementia to their baseline level of cognitive functioning following delirium, although cognition-focused approaches hold promise based on evidence of retained brain plasticity in persons with dementia. The benefits of cognition-focused approaches are supported in many studies, but some research demonstrates no benefit following such intervention. Moderators of treatment effect characterize individuals most likely to benefit from a given intervention, and these characteristics may help explain some of the inconsistencies in results.

Personality describes an individual's generally stable pattern of thinking, feeling, and behaving throughout one's lifetime. Personality traits have been consistently linked to intervention outcomes, including among individuals with dementia. However, the influence of personality on cognition-focused intervention outcomes for individuals with dementia and delirium experiencing acute cognitive decline has not been explored. Non-pharmacologic interventions are urgently needed for this population in order to optimize cognitive functioning as well as avoid the significant societal costs that accompany progressive functional loss.

Delirium, unlike dementia, has the potential to resolve. Therefore, this state of acute cognitive decline provides an opportunity to investigate the effects of a cognition-focused intervention in a considerably shortened period of time and possibly with more dramatic results. In effect, this approach provides an opportunistic model of how a cognition-focused approach might influence cognitive function in a population that is particularly susceptible to accelerated cognitive decline: individuals with dementia who are experiencing delirium. Existing research has failed to investigate the potential moderating influence of personal characteristics on the treatment effect of cognition-focused interventions. Identifying individuals who are best candidates for cognition-focused treatments may

allow for more precise development and targeting of these interventions and improve the effect size of future investigations.

Purpose of the Study

The purpose of this study was to determine whether personality moderated cognition-focused intervention outcomes in individuals at high risk for accelerated cognitive decline, i.e. those with dementia and delirium. Specifically, this exploratory study tested the moderating effects of five personality traits that comprise the five-factor model (neuroticism, extraversion, openness, agreeableness, conscientiousness; McCrae & John, 1992) on improvement in cognitive functioning and intervention engagement during a cognitive stimulation intervention. The following research questions were explored:

1. Does premorbid personality moderate the relationship between a cognitive stimulation intervention and improvement in four domains of cognitive function (attention, memory, orientation, and executive function) during a period of acute cognitive decline in persons with dementia?
2. Is premorbid personality associated with engagement in a cognitive stimulation intervention during a period of acute cognitive decline in persons with dementia?

Conceptual Framework

This study was guided by the theory of cognitive reserve (Stern, 2002, 2006, 2009, 2012). The conceptualization of *reserve* is common to many aspects of physiology and refers to the variability in which damage may occur to an organ before clinical symptoms appear (Sachdev & Valenzuela, 2009). Individuals are known to demonstrate differing levels of reserve capacity in the presence of organ damage, such as to the kidneys or liver. Similarly, the concept of reserve has been applied to degenerative brain conditions including AD. This theoretical perspective regarding the expression of cognitive impairment was developed based on empirical evidence that the clinical presentation of AD is

often inconsistent with the extent of neuropathology observed on autopsy (Katzman, et al., 1988; Neuropathology Group, 2001; Stern, 2002). Katzman et al. (1988) were the first to demonstrate that some individuals with higher levels of AD pathology on autopsy were cognitively normal during life, and furthermore, these individuals had a larger number of neurons compared to those who did express clinical symptoms. This was described as “greater reserve” against brain insult. Cognitive function, therefore, is not solely based on the degree of dementia pathology, but is dependent upon the varying capacities of individuals to withstand brain injury before the manifestation of clinical dementia symptoms (Whalley, Deary, Appleton, & Starr, 2004). The following summary will describe the theory of cognitive reserve including its relationship to mechanisms underlying a cognitive stimulation intervention.

Major Concepts of Cognitive Reserve Theory

Reserve is a broad descriptor of individual variation in protective capacity for damage, and is further divided into *brain reserve* and *cognitive reserve* (Stern, 2006). This distinction is based on brain reserve being attributed to passive physical brain attributes and cognitive reserve representing an active attempt by the brain to cope with pathology. Although conceptualized as independent, both are involved in the clinical presentation of cognitive deficits and together contribute to the expression of symptoms in the presence of AD and other pathology. Figure 1.1 introduces the hierarchy of the major concepts of reserve theory: brain reserve, cognitive reserve, neural reserve, and neural compensation. The following summary will define these concepts and relate them to the study purpose.

Figure 1.1. Major Concepts of Cognitive Reserve Theory

Reserve		
Brain Reserve (Passive)	Cognitive Reserve (Active)	
	Neural Reserve	Neural Compensation

Brain Reserve. *Brain reserve* is a passive model of reserve, also called a threshold model (Satz, 1993; Stern, 2002). Since early studies attributing brain reserve to higher head circumference or width (Graves, Mortimer, & Larson, 1996; Jorm, et al., 1997), the brain reserve concept has developed to refer to multiple structural brain properties that provide protection from insult including individual differences in brain volume, number of neurons, and number of synapses (Stern, 2006).

The level of brain reserve influences cognition such that larger, more developed brain networks are able to withstand more damage before the demonstration of clinical deficits (Stern, 2009). Individuals differ in their level of *brain reserve capacity*, or the ability to sustain insult prior to clinical manifestation of symptoms. When brain reserve capacity is exhausted beyond a physiological threshold determined by brain anatomy, clinical expression of deficit is evident. Within the passive brain reserve model, each individual possesses an innate threshold beyond which a certain level of brain damage will lead to impairment. However, this model does not account for individual differences in brain processing itself in the presence of damage. It considers the quantitative influence of brain damage only; instances of damage are considered additive but qualities of the damage itself are not considered. Therefore, brain reserve is considered in conjunction with the active model of reserve, cognitive reserve.

Cognitive Reserve. While brain reserve refers to actual brain physiology, *cognitive reserve* refers to individual brain organization, processing of information, and use of structural components in an active attempt to cope with brain damage (Stern, 2009). Individuals with more effective processing and compensatory approaches possess higher levels of cognitive reserve; this, in turn, makes them more successful at coping with brain damage even when brain reserve capacity is held constant (Liberati, Raffone, & Olivetti Belardinelli, 2011; Stern, 2006; Valenzuela & Sachdev, 2009). Therefore, cognitive reserve is considered an active model of reserve (Stern, 2006). In contrast to viewing cognitive deficit as breach of a static threshold, cognitive reserve considers functional impairment to be based on multiple factors which contribute to tolerance for and adaptation to brain insult.

Neural reserve and neural compensation. Cognitive reserve is further divided into neural reserve and neural compensation which describe the processes of active reserve. Both are potential mechanisms through which neuronal networks contribute to cognitive reserve, and likely are jointly responsible for the demonstrated protective effects (Steffener, Reuben, Rakitin, & Stern, 2011).

Neural reserve refers to the inter-individual variability in the efficiency and capacity of the healthy brain that underlies task performance (Stern, 2006). It is specifically concerned with existing functional brain networks (Steffener, et al., 2011). Due to the unique approaches to cognitive demands among individuals, there is extensive variability in the use of healthy brain networks during a given cognitive task. For example, while one individual may know the solution to a given cognitive challenge, the lifetime experience of another may have developed the networks necessary to achieve the same task in three different ways. The established functional brain networks of the latter yield a higher level of neural reserve. In the presence of brain pathology, the capacity to employ a variety of networks to achieve the same goal may assist the individual in coping with the deficit. If brain networks are more efficient and have greater capacity, neural reserve is higher and brain pathology is less disruptive (Stern, 2006, 2009). Therefore, neural reserve refers to the ability of an individual to cope with the disruption of brain pathology based on his or her innate ability for brain processing during cognitive tasks. The ability to maintain functional ability in the presence of AD pathology is increased with higher neural reserve, but this does not imply alterations in previously established brain networks. Rather, neural reserve provides for the more effective use of pre-existing networks.

Neural compensation refers to the inter-individual variability in active compensation for the disruption of standard processing by brain pathology (Steffener, et al., 2011; Stern, 2009). When the standard structures or networks normally used for cognitive processing are disrupted, the use of alternate brain networks may help maintain function or improve performance. Therefore, neural compensation is specific to compensatory processes in the face of injury or pathology. For example, an

individual may have always successfully achieved a given cognitive task in a certain way. The presence of brain pathology interrupts this series of networks, making task completion impossible. If this individual, in the face of the limitations imposed by the pathology, is able to successfully utilize an alternate brain network to achieve success, neural compensation has occurred. Therefore, the approach and networks employed were novel and directly resulted from the presence of impairment imposed by pathology. It is this hypothesized compensatory ability that may explain the mechanisms by which a cognitive intervention improves the cognitive ability of persons with dementia. While neural reserve describes inter-individual variability in the efficiency, capacity, and flexibility of brain networks, neural compensation describes inter-individual variability in the ability to compensate for brain damage through the use of brain structures or networks not typically utilized in intact brains (Stern, 2009).

Factors influencing cognitive reserve. Cognitive reserve describes the brain's ability to cope with pathology based on each individual's developed approach to cognitive processing as well as use of compensatory mechanisms (Stern, 2006, 2009). More sophisticated or effective processing approaches are thought to be developed over a lifetime's experience. Brain plasticity, or the ability of the brain to expand and establish neuronal connections when exposed to mentally stimulating activities (Vance, et al., 2008), is thought to contribute significantly to the ability to build cognitive reserve (Bach-y-Rita, 2003). Vance and Crowe (2006) propose, in their model of plasticity and cognitive reserve, that exposure to stimuli that promote learning or challenge existing neuronal connections leads to morphological changes in the brain. When activities stimulate cerebral activation, they are thought to produce physiological alterations such as increases in neuronal connections thereby leading to increased network efficiency and flexibility. It is through these processes that the improved ability for cognitive processing developed through life experience allows some individuals to cope with pathology, such as AD pathology, more effectively than others with the same structural brain characteristics (Stern, 2006).

Several lifestyle factors are known to be related to the risk of developing dementia, and therefore cognitive reserve. A systematic review of 22 longitudinal studies found that higher levels of education, occupation, and engagement in complex cognitive activities were associated with a 46% lower dementia risk compared to lower levels (Valenzuela & Sachdev, 2006a). Educational attainment has been researched most extensively and has repeatedly demonstrated that higher education levels are associated with a decreased risk of the clinical manifestation of dementia (Borroni, Alberici, Agosti, Premi, & Padovani, 2008; De Ronchi, et al., 1998; L. R. Hill, et al., 1993; Lindsay, et al., 2002; Qiu, Backman, Winblad, Aguero-Torres, & Fratiglioni, 2001). More highly educated individuals may possess more developed learning and cognitive strategies (Liberati, et al., 2011) and increased levels of neural connectivity due to their environmental experiences (Vance & Crowe, 2006). Occupational attainment is also related to dementia risk. Mentally demanding occupations are associated with decreased AD risk (Evans, et al., 1997; Karp, et al., 2004; Qiu, et al., 2003). Additionally, lifetime engagement in psychosocial and complex cognitive activities has also demonstrated associations with decreased dementia risk (D. A. Bennett, Schneider, Tang, Arnold, & Wilson, 2006; Crowe, Andel, Pedersen, Johansson, & Gatz, 2003; Richards & Sacker, 2003; Valenzuela & Sachdev, 2006a; Verghese, et al., 2003).

The multiple associations between lifestyle factors and clinical manifestation of dementia support a view of dynamic cognitive function in the presence of brain pathology; cognitive processes may be modified by experience through the mechanisms of plasticity, leading to increased cognitive reserve (Vance, 2006). High levels of cognitive engagement, as a result of a mentally stimulating lifestyle, are thought to promote more efficient and flexible strategies in response to cognitive tasks (Liberati, et al., 2011). This association has demonstrated a dose dependent relationship: increased participation in cognitive activities over a lifetime results in corresponding decreases in dementia risk (Valenzuela, et al., 2013; Valenzuela, et al., 2012; Valenzuela & Sachdev, 2006b; Verghese, et al., 2003). Thus, a cognitively engaging lifestyle promotes the building of cognitive reserve.

Personality traits, which are known to maintain general stability throughout the life course (Terracciano, Costa, & McCrae, 2006; Terracciano, McCrae, & Costa, 2010), affect behavior and preferences likely to influence activity and achievement during one's lifetime (McCrae & Costa, 2002) and therefore cognitive reserve. Indeed, high conscientiousness has been associated with an 89% reduction in AD risk (R. Wilson, Schneider, Arnold, Bienias, & Bennett, 2007). Alternatively, high neuroticism was determined to be an AD risk factor independent of pathological markers and was associated with an increased rate of cognitive decline in two studies (R. Wilson, et al., 2006; R. Wilson, et al., 2003). A recent analysis of 111 participants in the Baltimore Longitudinal Study of Aging, followed for up to 28 years including autopsy after death, found that low neuroticism and high conscientiousness increased resilience to clinical dementia even in the presence of AD pathology (Terracciano, et al., 2013). These results suggest that personality traits may influence the development of cognitive reserve.

Mechanisms of neural compensation. Compensatory use of alternate brain regions may include increased use of nearby brain areas during a task or the use of brain areas not typically associated with the task (Backman, et al., 1999; Becker, et al., 1996). These responses are thought to demonstrate plasticity of neural networks, which are altered presumably in response to cognitive demand. The mechanisms of plasticity are thought to include both functional modification of existing neuronal connections as well as structural changes such as new synapse formation or elimination (Feldman, 2009). Changes may occur at the cellular level through adaptation of neurons and supporting cells (Mattson, et al., 2002) or through adaptation of dendrites and synapses due to environmental stimuli (Greenwood, 2007). In the damaged brain, it is thought that these changes occur in response to the limitations imposed by brain pathology in an attempt to maintain functional ability. Retained plasticity mechanisms among those with cognitive impairments may be exploited through cognition-focused interventions, such as cognitive stimulation.

Research suggests that the capability for brain plasticity may be influenced by the apolipoprotein E (ApoE) gene. The ApoE ϵ 4 allele is the main genetic risk factor for AD (Ertekin-Taner, 2007) and is also associated with lower cognitive performance in cognitively intact carriers (Greenwood, Lambert, Sunderland, & Parasuraman, 2005). Carriers of the ApoE ϵ 4 allele may have inherently lower cognitive reserve due to an inability to utilize plasticity mechanisms to maintain cognitive performance in the presence of brain pathology.

Brain Reserve and Cognitive Reserve: Not Mutually Exclusive

Although brain reserve is discussed as passive, it is altered over time through reserve-building life experience that stimulates neurogenesis, resists apoptosis, and promotes plasticity (Stern, 2009). Brain anatomy is altered through these experiences, and the anatomical changes that result lead to increased brain reserve. Therefore, although life experiences are considered to be primary contributors to the building of cognitive reserve capacity, it is recognized that brain and cognitive reserve are not mutually exclusive. Factors that influence the development of cognitive reserve capacity may directly impact the physiology of the brain (Stern, 2006). Animal models have demonstrated the ability of cognitively stimulating environments to promote neurogenesis (Brown, et al., 2003; van Praag, Shubert, Zhao, & Gage, 2005) and potentially delay or slow the development of AD pathology (Lazarov, et al., 2005). Therefore, brain reserve is in fact partially modifiable by life experience such that the process of development and environmental interactions influence brain reserve over the lifespan including level of education, occupational complexity, and participation in complex mental activities (Valenzuela & Sachdev, 2006a). When levels of these environmental aspects are higher, brain reserve is gradually built and provides greater protection from damage.

Cognitive Reserve in Delirium and Dementia

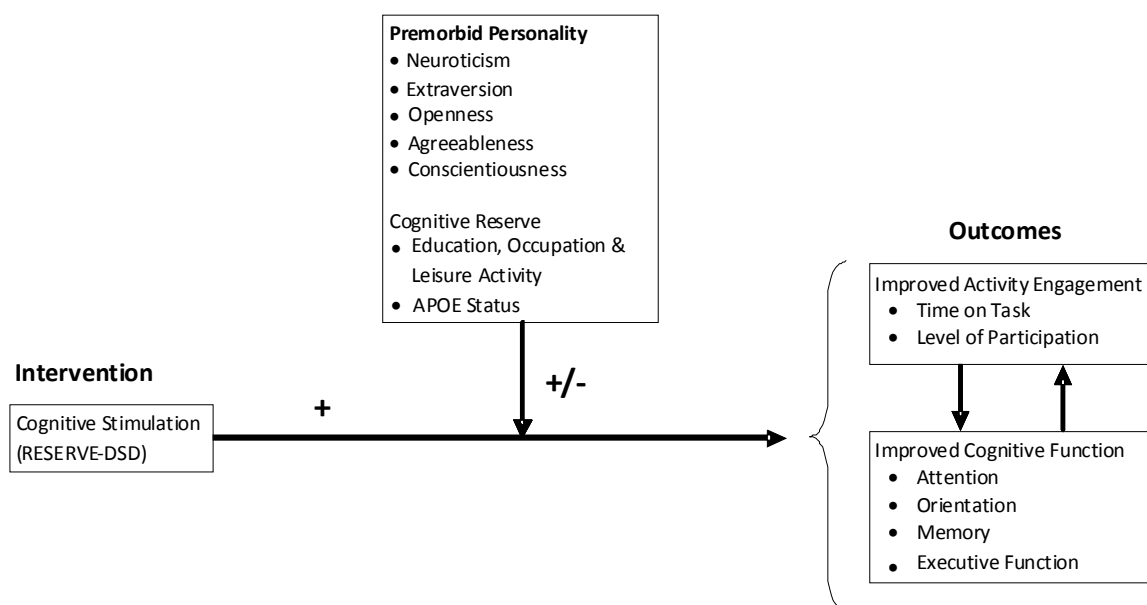
Dementia and delirium share commonalities in clinical presentation and pathology (Hshieh, et al., 2008), and have both been conceptualized as manifestations of decreased cognitive reserve

(Kolanowski, Fick, Clare, Therrien, et al., 2010; Stern, 2009). Pre-existing dementia is the leading risk factor for delirium (Cole, 2004; Inouye, 2006); therefore, decreased or exhausted cognitive reserve capacity may increase the risk for delirium development under precipitating conditions. Furthermore, when delirium occurs in individuals with AD, the rate of subsequent cognitive decline has been found to increase substantially (Fong, Jones, et al., 2009). This suggests that an acute onset of delirium may decrease cognitive reserve with long-term implications, leading to an accelerated trajectory of dementia-related cognitive decline. Educational attainment (Jones, et al., 2006) and participation in leisure activities (Yang, et al., 2008), both proxies of cognitive reserve, have been shown to decrease the risk of delirium in hospitalized older adults. Emerging evidence supports the role of cognitive reserve in not only the manifestation of dementia, but also the incidence of delirium among older adults.

Hypothesized Model for the Effect of RESERVE-DSD and Selected Moderator

A hypothesized model for the effect of the intervention (RESERVE-DSD) as well as the influence of the primary moderator of interest, premorbid personality, is shown in Figure 1.2. RESERVE-DSD provides cognitively stimulating activities that promote cognitive processing in four domains: attention, orientation, memory, and executive function (Kolanowski, Fick, Clare, Steis, et al., 2010). These activities are thought to stimulate brain plasticity via cognitive processing, improve cognitive function, and reduce the severity and duration of delirium. It is theorized that enhanced synaptic processes contribute to neural compensation when cognitively challenging activities are provided (Vance, Roberson, McGuinness, & Fazeli, 2010). Neural compensation, in turn, builds cognitive reserve (Stern, 2009) and therefore results in improvement in multiple outcomes: engagement in the cognitive intervention as a result of increased attention and improved cognitive function in the five targeted domains.

Figure 1.2. Hypothesized Model



Within the model, personality is considered a moderator of treatment (RESERVE-DSD) effect. Moderators influence the degree or direction of an effect (Shadish, Cook, & Campbell, 2002) and provide for characterization of individuals most likely to respond to a particular treatment (Baron & Kenny, 1986). It is hypothesized that premorbid personality, or personality prior to the onset of cognitive impairment, influences activity preferences (Caspi, Roberts, & Shiner, 2005; Friedman, 2000), motivation for participation (Judge & Ilies, 2002), performance (Elmstahl, Sommer, & Hagberg, 1996), and treatment adherence (Hurtz & Donovan, 2000; Judge & Ilies, 2002) within the RESERVE-DSD intervention.

Premorbid personality as a moderator of RESERVE-DSD. The influence of personality over a lifetime contributes to activity interests, motivation for personal and professional achievement, and the development of the quantity and quality of social networks (Wiggins, 1996). Personality encompasses the *basic tendencies* of individuals, their capacities and dispositions which may be inherited or influenced by life experience. These basic tendencies are manifested as *characteristic adaptations*:

acquired skills, habits, attitudes, and relationships as a result of interactions with the environment (McCrae & Costa, 1996). Therefore, the patterns of thoughts, feelings, and behaviors which describe personality directly influence interaction with and response to the environment. For example, a basic lifelong tendency to be highly conscientious leads to a characteristic adaptation of goal attainment and motivation in educational and professional pursuits (McCrae & Costa, 2010). It is hypothesized that the influence of personality on the interaction of an individual with his or her environment is a significant contributor to participation in cognitively stimulating activities.

The moderating influence of personality on health and treatment outcomes is well-established in other populations (B. Chapman, Duberstein, & Lyness, 2007; Conner, et al., 2007; Robb, Small, & Haley, 2008). The mechanisms of these effects are thought to be multi-factorial including personality's influence on stress response (Carver & Connor-Smith, 2010; J. E. Graham, Christian, & Kiecolt-Glaser, 2006), health-promoting or risky health behaviors (Bogg & Roberts, 2004; Caspi, et al., 2005), and lifestyle patterns including environment, situation, and relationship selection (Buss, 1987; Caspi, et al., 2005; Friedman, 2000). Although some degree of personality change may occur during dementia progression (Robins Wahlin & Byrne, 2011), empirical evidence supports the maintenance of rank-order stability of personality traits throughout the early stages (e.g., Chatterjee, Strauss, Smyth, & Whitehouse, 1992; Dawson, Welsh-Bohmer, & Siegler, 2000; Siegler, et al., 1991). This indicates that individuals maintain stability in personality, overall, in relation to other individuals. Therefore, personality-based preferences, behaviors, and tendencies continue to exert their influence among persons with early-stage dementia.

Influence of personality on cognitive reserve. Within the hypothesized model, personality can also be considered a contributor to the development of neural reserve, and therefore cognitive reserve, over one's lifetime. Interaction with one's environment is influenced by personality (McCrae & Costa, 1996). These interactions directly influence lifestyle factors and behavior, such as activity preferences

and social interactions, which contribute to cognitive reserve (e.g., D. A. Bennett, et al., 2006; Valenzuela & Sachdev, 2006a). Participation in cognitively and socially stimulating activities over one's lifetime leads to increased efficiency and responsiveness of brain networks (Moore, Cohen, & Ranganath, 2006; Olesen, Westerberg, & Klingberg, 2004). Therefore, the established patterns and preferences for reacting to environmental stimuli (personality) are considered within the model to influence the efficiency, flexibility, and capacity of individuals to respond to cognitive demands (neural reserve).

Theoretical Definitions

The following definitions are used in this study:

Dementia: Inclusive of all causes, is diagnosed when cognitive or behavioral symptoms: 1) interfere with the ability to function at work or at usual activities; and, 2) represent a decline from previous levels of functioning and performing; and 3) are not explained by delirium or major psychiatric disorder. These impairments must include at least two of the following: impaired ability to acquire and remember new information; impaired reasoning and handling of complex tasks, poor judgment; impaired visuospatial abilities; impaired language functions (speaking, reading, writing); changes in personality, behavior or comporment (McKhann, et al., 2011).

Delirium: An acute disturbance of consciousness with a fluctuating course and further characterized by reduced attention, memory deficit, disorientation, language disturbance, and perceptual disturbance. These changes must be due to a direct physiologic cause, medical condition, intoxication, medication, or multiple causes, and are not otherwise attributable to dementia (American Psychiatric Association, 2000).

Cognition-Focused Interventions: Non-pharmacological approaches that target cognitive processing in an attempt to improve functioning. These include cognitive stimulation, cognitive training, cognitive rehabilitation, and multi-component approaches (Clare & Woods, 2003)

Cognitively Stimulating Intervention: A non-regimented intervention consisting of recreational activities designed to support attentional capacity and stimulate cognitive processing (Clare & Woods, 2003).

Activities are individually tailored based on functional abilities and interests and promote processing in multiple cognitive domains (Kolanowski, Fick, Clare, Therrien, et al., 2010).

Brain Reserve: Individual differences in the brain itself which allow some people to cope better than others with brain pathology, i.e. structural differences such as brain size, number of neurons, and number of synapses (Stern, 2009).

Cognitive Reserve: Individual differences in how people process cognitive tasks that allow some to cope better than others with brain pathology (Stern, 2009; Valenzuela & Sachdev, 2009). Cognitive reserve consists of two components: neural reserve and neural compensation.

Neural Reserve: Inter-individual variability in the efficiency or capacity of healthy brain networks which contribute to cognitive performance (Stern, 2009).

Neural Compensation: Inter-individual variability in the ability to compensate for disruption due to brain pathology by using brain structures or networks not normally used in intact brains (Stern, 2009).

Personality: The relatively enduring pattern of recurrent interpersonal interactions which characterize a human life (Sullivan, 1953).

Assumptions

The following assumptions are made in this study:

1. Older adults with dementia are susceptible to acute cognitive decline, or delirium, when faced with stressors.
2. Acute cognitive decline in individuals with dementia leads to increased vulnerability to accelerated cognitive decline.
3. Acute cognitive decline in individuals with dementia is reversible if effectively treated.

4. Interventions for delirium resolution have been largely unsuccessful and have not targeted specific mechanisms influencing cognitive functioning.
5. Cognition-focused interventions target brain plasticity as a mechanism to increase cognitive reserve.
6. Individual factors moderate intervention outcomes such that some individuals respond more positively to a particular treatment than others.
7. Personality is relatively consistent over time, across contexts, and throughout the early stages of dementia.
8. Personality influences individual preference for and engagement in cognitively and socially stimulating activities.
9. Personality contributes to cognitive reserve over the life course by building neural reserve through patterns of and preferences for activity.
10. Neural compensation can be induced by stimulating brain plasticity processes through a cognitively stimulating intervention.

Significance of the Study

This study examined the moderating influences of personality traits on the treatment effects of a cognitively stimulating intervention in older adults highly vulnerable to accelerated cognitive decline. The knowledge gained helps guide the science of cognition-focused interventions in several ways: (1) provide a critically needed foundation for future research; (2) assist with precise targeting of the intervention to best candidates; (3) inform personally tailored interventions for individuals with dementia to improve activity participation; and (4) enable understanding of the moderating effects of personality on cognition-focused intervention outcomes to inform accurate development and targeting of these interventions to those most likely to benefit.

Previous research has demonstrated the potential effectiveness of cognition-focused interventions in improving cognitive function in people with dementia. Therefore, this study applied emerging evidence regarding brain plasticity and cognitive reserve to people with dementia experiencing an acute decline in cognition. An acute cognitive change in this population may be an opportunity to see improvement in cognitive functioning over a shorter period of time, rather than the months or longer typically necessary for a cognitive intervention in dementia. Additionally, these individuals are particularly susceptible to accelerated cognitive decline and long-term negative consequences associated with acute cognitive decline.

Chapter 1 Summary

Cognitive decline associated with dementia among older adults is devastating and, at present, irreversible. Individuals with dementia are highly susceptible to acute declines in cognitive status when faced with stressors such as illness or hospitalization, and these acute changes often lead to an accelerated trajectory of decline and associated negative outcomes. Effective interventions to return these individuals to their baseline level of cognitive functioning have not yet been developed, although cognition-focused interventions have demonstrated potential benefits in individuals with dementia. These interventions are thought to stimulate brain plasticity, thereby promoting compensatory processes that allow some individuals to improve cognitive processing.

This study was guided by a hypothesized model based on the theory of cognitive reserve as well as empirical evidence supporting the influence of the moderating factors of interest on intervention outcomes. The cognitively stimulating activity intervention implemented in this study was hypothesized to stimulate brain plasticity mechanisms leading to increased cognitive reserve via neural compensation, and thereby improved cognitive function outcomes. It was also hypothesized that individuals vary in their response to treatment due to premorbid personality traits. The influence of personality traits on environmental interactions also influences cognitive reserve. Therefore, an individual's lifelong

preferences and behaviors influence present participation in cognitively stimulating activities, but also contribute to one's long-term risk for cognitive decline and potentially intervention benefit.

In order to determine who may benefit most from cognition-focused interventions, the consideration of moderating variables is necessary to explore the relationships between treatment and outcomes with more precision. Explicating these associations helps to determine individuals who are the best candidates for particular interventions, thereby maximizing treatment effect. Personality is a well-established moderator of health outcomes and treatment effects across multiple populations and conditions. Furthermore, personality has been shown to influence the outcome of activity interventions among persons with dementia. Although evidence supports the potential influence of personality traits on non-pharmacological treatment outcomes in individuals with dementia, their moderating effect on cognition-focused intervention for delirium outcomes has not been explored. This study addressed this gap in knowledge in order to improve the empirical foundation for personally-tailored, cognition-focused interventions for individuals with dementia and delirium.

Chapter 2

Review of the Literature

Optimal cognitive functioning in older adults is a public health priority as well as a major determinant of self-reported healthy aging (Centers for Disease Control and Prevention & The Alzheimer's Association, 2007; Laditka, et al., 2009). Many older adults are at risk for debilitating cognitive decline due to age-related neurodegenerative disease such as Alzheimer's disease (AD) or other dementias. Furthermore, individuals with dementia are highly susceptible to an acute decline in cognitive functioning, or delirium, when faced with a stressor such as illness or hospitalization (Fick, et al., 2002). Acute cognitive decline in this already vulnerable population is associated with significant negative consequences including a hastened dementia trajectory. At present, no cure is available to reverse dementia-related cognitive decline, but rehabilitation to optimize cognitive functioning is a realistic goal (B. Wilson, 2008) and there is evidence that delirium can be reversed if effectively treated (Fong, Tulebaev, et al., 2009).

Cognition-focused interventions are non-pharmacological approaches that target cognitive processing in an attempt to improve functioning. They have been tested in older adults with dementia and hold promise for individuals experiencing cognitive decline; however, they have demonstrated mixed success across studies (e.g., Buschert, Bokde, & Hampel, 2010; Clare, et al., 2010; Clare & Woods, 2003; Papp, et al., 2009; Spector, et al., 2003; Wolinsky, et al., 2006). It is unknown whether some individuals are better candidates for cognition-focused interventions compared to others, which may account for a portion of the variability in results. Personality's influence on health outcomes such as participation in and benefit from other behavioral interventions is well-established (e.g., Benjamin Chapman, 2007; Conner, et al., 2007; Franks, et al., 2009; Judge & Ilies, 2002; Paika, et al., 2010; Rossi, et al., 2007), but the relationship between personality and the outcome of cognition-focused interventions for dementia is not known. This study investigated personality as a moderator of the

treatment effect of a cognitively stimulating activity intervention for older adults at high risk for accelerated cognitive decline.

The following literature review will evaluate and synthesize the scientific evidence regarding: 1) relationship between dementia and delirium; 2) brain plasticity and cognitive reserve in dementia and delirium; 3) cognition-focused interventions for cognitive decline; 4) personality and cognitive decline; and, 5) personality as a moderator of health-related outcomes.

Relationship between Dementia and Delirium

Dementia and delirium are distinct clinical diagnoses, but share commonalities in both clinical presentation as well as underlying pathological mechanisms (Hshieh, et al., 2008). In fact, it has been suggested that they are both manifestations of common underlying brain vulnerability rather than two separate conditions (Fick, et al., 2009; Hshieh, et al., 2008; Inouye & Ferrucci, 2006; Murray, et al., 1993). The following review will provide clinical definitions that distinguish dementia and delirium to enhance clarity in discussion of the evidence base for this study; however, the extensive interrelationships between these conditions are highlighted. It is these associations and commonalities that support the view that delirium in persons with dementia represents the exacerbation of cognitive deficits in an already vulnerable population.

Diagnostic Distinctions of Dementia and Delirium

Dementia is a syndrome of chronic decline in memory and at least one other cognitive domain such as language or visuospatial ability; these deficits are severe enough to interfere significantly with social or occupational functioning (American Psychiatric Association, 2000; Reuben, et al., 2010). Onset is gradual, decline is progressive, and deterioration is usually irreversible. The underlying pathology of dementia is due to a variety of causes, the most common of which is AD. Several other causes include vascular dementia, frontotemporal dementia, and dementia with Lewy bodies, although individuals often have pathological features of more than one of these disorders simultaneously (Armstrong, et al.,

2005). Based on empirical evidence demonstrating mixed pathologies on autopsy, it is now recognized that a clinical diagnosis of AD may represent an accumulation of multiple pathologies, including cerebrovascular disease most frequently (Aguero-Torres, et al., 2006; Armstrong, et al., 2005; Richards & Brayne, 2010).

Delirium is an acute clinical syndrome characterized by fluctuating level of consciousness and pervasive impairment in mental, behavioral, and emotional functioning (American Psychiatric Association, 2000). In contrast to dementia, it is transient and potentially reversible, although it may become chronic or cause permanent disability if untreated (Fong, Tulebaev, et al., 2009). The highest rates of delirium are in hospitalized older adults, prevalence increases with age, and it is associated with a downward spiral of events leading to loss of independence, decreased functional ability, declines in health status, and death (Inouye, 1998, 2006; Kiely, et al., 2009). Delirium etiology is considered multifactorial due to both predisposing and precipitating factors (Inouye, 1999). Individuals may be predisposed to delirium development due to risk factors such as advanced age, cognitive impairment or dementia, severe illness, dehydration, constipation, hypoxia, immobility, infection, or sensory impairment (Inouye, 1999; Young, et al., 2010). When a vulnerable individual is exposed to a precipitating factor such as physical restraints, a urinary catheter, or the addition of multiple medications, delirium may result (Inouye, 1999).

Significance of Delirium in Individuals with Dementia

Dementia is the leading risk factor for delirium (Cole, 2004; Inouye, 2006). The prevalence of delirium in those with preexisting dementia ranges from 32% to 89% in hospital settings, and a need for improved prevention, recognition, and management has been identified (Fick, et al., 2002). Among individuals admitted to post-acute care facilities following hospitalization, an average of 1 in 7 met criteria for delirium with rates ranging from 1 in 4 to 1 in 15 across facilities (Jones, Kiely, et al., 2010).

Individuals with dementia who develop delirium are susceptible to many negative outcomes including accelerated cognitive and functional decline, decreased quality of life, as well as increased morbidity and mortality (Fick & Foreman, 2000; Francis & Kapoor, 1992; Inouye, Rushing, Foreman, Palmer, & Pompei, 1998; Levkoff, Besdine, & Wetle, 1986; Rockwood, et al., 1999). Older adults with dementia who develop delirium during hospitalization have demonstrated more than twice the mortality risk after discharge compared to those with dementia or delirium alone (Bellelli, et al., 2007). Multiple additional adverse events have been associated with delirium in these individuals including hastened progression of dementia, prolonged hospitalization, re-hospitalization, and institutionalization (Fick, et al., 2002; Fick & Foreman, 2000; Inouye, 1994; Inouye, et al., 1998; Rockwood, et al., 1999). Resolution of delirium in post-acute care is critical to recovery of function. When delirium is resolved within two weeks of admission to post-acute care, complete functional recovery to pre-hospital level is realized; however, when delirium is not resolved, less than 50% of pre-hospital functioning is recovered (Kiely, et al., 2006).

In addition to the poor outcomes experienced by individuals with dementia who develop delirium, the societal cost cannot be overlooked. Health care costs and utilization are significantly higher for these individuals when compared to both individuals without dementia or delirium as well as those with dementia alone (Fick, Kolanowski, Waller, & Inouye, 2005). Hospitalized patients with delirium are over two times more expensive to care for than patients without delirium, with delirium-specific costs ranging from approximately \$16,000 to \$64,000 per patient over a period of one year (Leslie, et al., 2008). Healthcare costs are directly related to functional impairments in persons with dementia: costs increased by almost \$2000 for each additional impairment in activities of daily living (ADLs) and by over \$500 for each additional impairment in instrumental ADLs (J. Hill, Fillit, Thomas, & Chang, 2006). Therefore, the ability to restore function to pre-hospitalization levels by timely resolution of delirium not only benefits the individual, but also the healthcare system overall.

Associations between Dementia and Delirium

Due to multiple interrelationships and pathophysiological similarities between dementia and delirium, it has been suggested that the conditions are representations of a common underlying cognitive disorder (Hshieh, et al., 2008; Inouye, 2006; Murray, et al., 1993). There is a relationship between the degree of pre-existing cognitive impairment and delirium such that individuals with a higher level of cognitive dysfunction demonstrate an increased severity of delirium symptoms in most cognitive domains (Voyer, McCusker, Cole, & Khomenko, 2006). Increased severity of previous cognitive impairment is also associated with delirium prevalence (Voyer, Cole, et al., 2006) and pre-existing dementia often increases the duration of delirium (Dasgupta & Hillier, 2010). Thus, individuals with dementia develop delirium more readily than cognitively intact older adults.

Delirium in older adults is associated with an increased risk of dementia, including after controlling for age, gender, comorbidities, and illness severity (Jackson, Gordon, Hart, Hopkins, & Ely, 2004; Witlox, et al., 2010). Therefore, while individuals with dementia are predisposed to delirium, older adults with delirium are also at greater risk of developing dementia in the future. These mechanisms are not yet understood, but it is known that delirium symptoms may persist for up to a year or longer after initial presentation (Levkoff, et al., 1992; Marcantonio, Flacker, Wright, & Resnick, 2001; McCusker, Cole, Dendukuri, Han, & Belzile, 2003). Additionally, long-term cognitive decline (Jackson, et al., 2004) and loss of the ability to perform ADLs (Murray, et al., 1993) may occur after delirium. This evidence further supports the overlap between dementia and delirium; the lines may be blurred between delirium-related impairment and the manifestation of dementia symptoms after an incident of delirium.

The development of delirium in people with AD also accelerates cognitive decline, at a rate three times faster than those with AD who do not experience a delirium (Fong, Jones, et al., 2009). A recent study examined the delirium and long-term cognitive trajectories; they found that delirium among hospitalized older adults with AD was associated with an increased risk of cognitive deterioration

that persisted for up to five years (Gross, et al., 2012). These findings imply that although delirium begins with an acute onset of cognitive decline, it predisposes an individual to long-term impairment, including dementia, and worsens the trajectory of decline in those with pre-existing dementia. Although dementia and delirium are considered distinct clinical syndromes, primarily due to differences in presentation such as chronic development versus acute onset, the degree of interrelationship between the conditions indicates blurring of these boundaries.

Pathogenic Commonalities between Dementia and Delirium

The multiple associations between dementia and delirium may be attributed, at least in part, to common pathologic mechanisms influencing their development and progression. Developing evidence supports shared pathophysiological mechanisms in dementia and delirium including inflammation, reduced cholinergic activity (Inouye & Ferrucci, 2006; Simone & Tan, 2010), as well as a common genetic risk factor, the ApoE ϵ 4 allele (Utermann, 1994; B. van Munster, Korevaar, Zwinderman, Leeflang, & de Rooij, 2009). Conclusive evidence regarding the exact pathological processes underlying delirium development, in individuals with or without pre-existing dementia, is not yet available, but emerging science has developed a persuasive evidence base for consideration of these factors.

At present, cholinergic deficiency is the leading hypothesis regarding the mechanism of delirium (Hshieh, et al., 2008; Inouye, 2006). Significant cholinergic dysfunction has long been associated with dementia (Bartus, Dean, Beer, & Lippa, 1982) and present research substantiates the role of cholinergic deficiency in AD (Rakonczay, Horvath, Juhasz, & Kalman, 2005). The evidence regarding the association between delirium and cholinergic deficiency is largely based on studies examining the effects of anticholinergic medications on cognition in general and delirium specifically. A recent systematic review examined 27 studies published since 1966 in which anticholinergic activity of medications and the effect on older adults' cognitive function were examined (Campbell, et al., 2009). The authors found a consistent association between the use of anticholinergic medications and cognitive impairment in older

adults as well as anticholinergics and delirium. Similarly, serum anticholinergic activity has consistently been associated with decreases in cognitive function, including delirium development, in people with dementia (Chew, Mulsant, & Pollock, 2005; Konishi, et al., 2010).

Inflammatory processes are thought to play a role in both dementia progression as well as delirium development (Simone & Tan, 2010). Chronic inflammation is associated with neurodegenerative disease, including AD (Y.-J. Lee, Han, Nam, Oh, & Hong, 2010), and acute conditions that cause high stress or an inflammatory response, such as hospitalization, infection, or surgery, are associated with delirium (Simone & Tan, 2010). In multiple studies, increased pro-inflammatory cytokine levels (mediators of the body's immune response) have been associated with a higher risk of AD (McGeer & McGeer, 2001; Yucesoy, et al., 2006) as well as delirium (Holmes, et al., 2009). Additional studies have also demonstrated elevated levels of pro-inflammatory cytokines in delirium (de Rooij, van Munster, Korevaar, & Levi, 2007; Kudoh, Takase, Katagai, & Takazawa, 2005; B. C. van Munster, et al., 2008), AD (Licastro, et al., 2000; Tan, et al., 2007; Yaffe, et al., 2003), and non-AD dementias (Sundelof, et al., 2009).

The apolipoprotein E (ApoE) gene, and specifically the ApoE ϵ 4 allele, is widely accepted to be the one consistent risk factor for late-onset AD (Bettens, Slegers, & Van Broeckhoven, 2010; Coon, et al., 2007). ApoE plays multiple roles, one of which is an association of ApoE ϵ 4 with a reduction in cholinergic activity in the brain (Trzepacz, 2000). Evidence supporting the role of ApoE ϵ 4 in delirium is growing, and a recent prospective cohort study and meta-analysis integrated the current knowledge regarding an association between ApoE ϵ 4 and delirium while also adding additional evidence to the literature (B. van Munster, et al., 2009). Previous studies that demonstrated no association between ApoE ϵ 4 and delirium used smaller sample sizes and therefore may not have had sufficient power to detect an effect (e.g., Adamis, et al., 2007; Ely, et al., 2007); therefore, the van Munster et al. (2009) meta-analysis combined current data with former studies to examine associations in aggregate

(n=1,099). They found that ApoE ϵ 4 allele was associated with delirium, particularly in patients admitted for non-cardiac surgeries. After adjusting for age, cognitive impairment, and functional impairment, the odds ratio for the risk of delirium in ApoE ϵ 4 carriers compared to non- ApoE ϵ 4 carriers was 1.59, indicating that these individuals had 1.59 times the risk of developing delirium.

Summary: Relationship between Dementia and Delirium

In summary, although delirium and dementia have historically been considered clinically distinct, the extensive interrelationship between the two conditions as well as evidence supporting the potential for shared mechanisms in their expression indicates blurred boundaries and a degree of overlap. Although the pathological mechanisms underlying both delirium and dementia are yet to be definitively described, multiple pathogenic factors are commonly involved in dementia progression and delirium development including inflammatory processes and deficiency in cholinergic activity. The ability to investigate genetic risk factors in the development of delirium has resulted in interesting evidence that supports the role of the ApoE ϵ 4 allele in not only AD, but also delirium. Across bodies of evidence, the interrelationships between dementia and delirium are substantial. It is likely that the manifestation of both dementia and delirium are the result of multiple mechanisms, but the overall commonalities between the two conditions suggest shared pathology.

Cognitive Reserve, Dementia, and Delirium

Cognitive reserve theory was introduced as a guiding framework for the conceptual model for this study, but it is also based on a growing body of evidence supporting its role in the expression of both dementia and delirium. Cognitive reserve refers to the hypothesized differences between individuals in their susceptibility to brain insult, such as AD pathology (Stern, 2012). It is typically operationalized as an active cognitive lifestyle including education, occupation, and complex mental activities throughout the lifespan. The related concept of brain plasticity is also important to the investigation of intervention approaches. The following section will present the evidence regarding the

role of cognitive reserve in individuals with dementia, its relationship to the further development of delirium, and the maintenance of brain plasticity in individuals with dementia.

The Role of Cognitive Reserve in Dementia

According to the cognitive reserve hypothesis, building cognitive reserve over one's lifetime is thought to provide protection against brain insult such as AD pathology, resulting in delayed clinical manifestation (Stern, 2006, 2012). A variety of lifestyle factors are associated with higher levels of cognitive reserve including premorbid intelligence, educational level, reading ability, and occupational attainment (Helzner, Scarmeas, Cosentino, Portet, & Stern, 2007; Marioni, van den Hout, Valenzuela, Brayne, & Matthews, 2012; Scarmeas & Stern, 2004; Stern, 2002; R. Wilson, et al., 2000). Overall, a more cognitively engaging lifestyle is thought to provide protection against the manifestation of dementia symptoms. The factors influencing cognitive reserve are likely multiple and interconnected.

An extensive meta-analysis of 22 longitudinal cohort studies examined the influence of cognitive activity over the life span on dementia risk (Valenzuela & Sachdev, 2006a). Included studies were prospective and measured dementia incidence as well as various proxies of cognitive reserve (such as education or occupation) for a total of over 29,000 individuals. Findings demonstrated that higher cognitive reserve was associated with a 46% reduction in dementia incidence. Furthermore, increased complex mental activity in late life was associated with lower dementia risk independent of other predictors, and a dose-response relationship existed between the extent of complex mental activity in late life and dementia risk. This indicates that increasing cognitive activity even in late life may provide benefit.

A more recent longitudinal study included 101 initially cognitively intact adults ages 75 to 85 participating in the Bronx Aging Study (Hall, et al., 2009). Participants self-reported daily cognitive activity at baseline and every 12 to 18 months following, until loss to follow-up or death. Cognitive activity was assessed according to participation in reading, writing, crossword puzzles, board or card

games, group discussions, or playing music. Results indicated that late life cognitive activities positively influenced cognitive reserve independently of education. Also, each additional self-reported day of cognitive activity at baseline delayed the onset of accelerated memory decline by 0.18 years. The effect of participation in cognitively stimulating leisure activities was found to be nearly identical to a previous investigation which showed that education delayed the onset of accelerated memory decline in those who developed dementia (Hall, et al., 2007).

The influence of multiple cognitive lifestyle factors on dementia incidence as well as survival was recently investigated in a longitudinal, population-based study of 13,004 individuals age 65 or older (Valenzuela, Brayne, Sachdev, Wilcock, & Matthews, 2011). Participants were followed over 10 years for dementia incidence and 12 years for mortality. A Cognitive Lifestyle Score was compiled based on cognitive activity during three stages of life. Cognitive activities assessed included education, occupational complexity, and social engagement. Results showed that the combination of education, occupational complexity, and late-life social engagement was an independent predictor of dementia risk (odds ratio = 0.6), rather than one component individually. Individuals with a higher Cognitive Lifetime Score were 40% less likely to develop dementia. In a related study (Valenzuela, et al., 2012), the Cognitive Lifestyle Scores were associated with increases in cortical thickness and density in the prefrontal lobe, which may indicate a biological mechanism for the protective effects of an active cognitive lifestyle.

The influence of cognitively stimulating activities on the rate of cognitive and functional decline in individuals with AD has also been recently examined (Treiber, et al., 2011). Individuals diagnosed with AD (n=187) participating in an ongoing longitudinal cohort study were followed semiannually for an average of 2.7(0.4) years. Caregivers provided information regarding frequency of participation in 31 leisure activities such as reading, attending cultural events, and listening to music. Global cognitive ability was assessed with the MMSE. Activities were further discriminated based on whether they

required active cognitive processing of novel information or were cognitively passive or receptive (e.g., watching TV). Results demonstrated that engagement in cognitively stimulating activities among individuals early in the course of AD was associated with slower cognitive decline ($p=.02$). A linear mixed model predicted that among those diagnosed less than one year ago, engagement in no cognitively stimulating leisure activities would be associated with a decline of 3.9 points per year on the MMSE. Alternatively, individuals engaged in five stimulating activities would decline by 2.2 points per year. This difference in rate of cognitive decline decreased substantially with duration of AD. Among individuals with a three-year duration of AD, a 2.2 point decline per year was predicted for those engaged in no activities versus a 2.1 point decline per year for engagement in five activities. Additionally, a higher number of cognitively stimulating activities was associated with better functional ability, particularly as dementia duration increased ($p=.006$). These results indicate that cognitive reserve may be positively influenced by cognitively stimulating activities after dementia onset, leading to slower cognitive decline and an improvement in physical functional ability.

The Role of Cognitive Reserve in Delirium

Lifestyle factors also may play a protective role via cognitive reserve in older adults with regard to delirium, and enhancing cognitive reserve may be effective in delirium prevention (Fick, et al., 2009; Jones, Fong, et al., 2010). A secondary analysis of two hospital-based studies examined the relationship between educational attainment and the risk of delirium among older adults (Jones, et al., 2006). Findings included a higher risk of delirium among individuals with fewer years of education; each year of completed education was associated with a 0.91 lower odds of delirium and individuals with seven years of education were 1.6 times as likely to develop delirium as those with 12 years of education. Education may be an important experience that enhances neural connectivity and the tendency to engage in mentally stimulating activities throughout life (Vance & Crowe, 2006).

The same cohorts of participants were used for an additional study examining the role of leisure activity prior to hospitalization (Yang, et al., 2008). The effects of both education and self-reported participation in activities on the risk for delirium during hospitalization were examined. Types of activities assessed included physical exercise, yard work, hobbies, entertainment activities, reading, working at a paid or volunteer job, regularly playing games, attending religious services, visiting friends, and participating in groups. Both education (odds ratio = 0.92) and activity (odds ratio = 0.60) were significant predictors of delirium incidence. Furthermore, activity participation was found to mediate the relationship between education and delirium; however, only participation in regular exercise was independently and significantly protective against delirium. These results suggest that higher baseline levels of education as well as activity participation may provide a protective effect (i.e., build cognitive reserve) and provide a buffer to the stressors associated with hospitalization that may result in delirium development.

Brain Plasticity as a Mechanism to Build Cognitive Reserve

Cognitive reserve is referred to as active reserve because it proposes that individuals possess varying abilities to utilize compensatory mechanisms in response to brain pathology (Stern, 2006). It is dynamic and modifiable (Sachdev & Valenzuela, 2009). Stern (2009) distinguishes the active compensatory processes leading to increased reserve as neural compensation. Mechanisms leading to these compensatory effects may be conceptualized as plasticity, or the dynamic capability of the brain to recruit additional or alternate brain sites (Duffau, 2006; Flicker, 2009). Plasticity theory posits that when individuals are exposed to novel or challenging activities, neuronal connections adapt and physiological changes to the brain result. When these adaptations are beneficial, neural connections are strengthened and expanded leading to an increase in cognitive reserve and therefore maintenance of cognitive ability (Vance & Crowe, 2006). The mechanisms of plasticity are thought to include both functional modification of existing neuronal connections as well as structural changes such as new

synapse formation or elimination of unnecessary connections (Feldman, 2009). In the damaged brain, it is thought that these changes occur in response to the limitations imposed by brain pathology in an attempt to maintain functional ability.

Evidence supporting the retained ability of individuals with early-stage dementia to utilize the compensatory processes of plasticity includes neuroimaging studies as well as investigations of cognitive plasticity in individuals with AD (e.g., Backman, et al., 1999; Becker, et al., 1996; Grady, et al., 2003; Hopper, Drefs, Bayles, Tomoeda, & Dinu, 2010; Pariente, et al., 2005; Spector, et al., 2003).

Neuroimaging studies provide evidence of compensatory brain activation: increased use of nearby brain areas during a task or the use of brain areas not typically associated with the task. These responses are thought to demonstrate plasticity of neural networks. In individuals with dementia-related pathology, differences in magnitude or patterns of brain activation when compared to cognitively normal adults are interpreted as evidence of a plasticity response.

The relationship between increased prefrontal brain activation and successful task performance in cognitively intact older adults and individuals with early-stage AD has demonstrated retained compensatory abilities. Grady et al. (2003) compared 24 subjects (12 cognitively normal, 12 with probable early-stage AD) for PET activation differences during performance on a set of memory tasks. PET scans demonstrated differences in brain activity between controls and AD subjects during task completion: the AD group demonstrated a more extensive recruitment of brain regions in response to task demands. Most importantly, this greater degree of activation correlated with improved task performance such that individuals with AD who demonstrated this response were able to perform the memory tasks with more accuracy than those who demonstrated less brain activation. Similarly, Pariente et al. (2005) compared fMRI results during a face-name recognition task in people with mild AD (n=12) compared to cognitively intact controls (n=17). Compared to the control group, subjects with AD demonstrated decreased activation in the hippocampus and simultaneously increased activation in the

parietal and frontal lobes during successful encoding and retrieval of information. This response was interpreted as effective compensation; the use of additional cognitive resources, unique to cognitively intact controls, was associated with better task performance.

Additionally, the capability for brain plasticity may be influenced by the ApoE gene. The ApoE ϵ 4 allele is the main genetic risk factor for AD and is also associated with lower cognitive performance in cognitively intact carriers (Ertekin-Taner, 2007; Greenwood, et al., 2005). Carriers of the APO4 allele may have inherently lower cognitive reserve due to an inability to utilize plasticity mechanisms to maintain cognitive performance in the presence of brain pathology. It has also been shown, however, that ApoE ϵ 4 carriers may be able to compensate for the deleterious genetic effects, at least partially, by building cognitive reserve through lifestyle activities (Garibotto, et al., 2012).

Summary: Cognitive Reserve, Dementia, and Delirium

Cognitive reserve is a theoretical construct supported by an evolving foundation of empirical evidence. Multiple studies support an association between lifestyle factors such as educational or occupational attainment and the risk for dementia which provides support for the concept of cognitive reserve. Complex cognitive activity, even in late life, may provide a protective effect against dementia-related cognitive decline. Similarly, higher levels of education and leisure activities in older adults may reduce the risk of delirium during hospitalization. These findings indicate that cognitive reserve may be increased, even among older adults, in order to provide protection against cognitive decline.

Plasticity is considered the major mechanism responsible for the building of cognitive reserve. It is through plasticity processes that neural compensation is thought to take place in the presence of dementia-related pathology. Evidence supports the ability of individuals with early-stage AD to utilize these compensatory mechanisms to recruit additional or alternate brain networks in order to maintain function in the face of cognitive demand.

Interventions for Dementia and Delirium

Based on the evidence supporting the beneficial effects of complex cognitive activity, providing mentally challenging or stimulating activities to individuals experiencing cognitive decline may stimulate plasticity and build reserve, thereby reducing the severity of clinical symptoms. *Cognition-focused interventions* have been tested in persons with dementia for their ability to slow or alter dementia progression and improve cognitive performance by targeting cognitive processing. *Cognitive stimulation* is a generalized approach to cognition-focused intervention consisting of a range of activities that promote cognitive processing with the aim of enhancing overall mental and social functioning (Clare & Woods, 2003). It is one of the most researched approaches to cognition-focused intervention in individuals with dementia and its benefits are supported by a sizable body of evidence (Aguirre, et al., 2013; e.g., Spector, Orrell, & Woods, 2010; Spector, Woods, & Orrell, 2008; Woods, et al., 2012).

Despite the negative patient outcomes and increased costs associated with delirium, development of therapeutic interventions for acute cognitive decline has been limited (Skrobik, 2010). Strategies are primarily focused on the prevention of delirium since avoiding onset is the most effective way to prevent associated complications (Inouye, 2006). Several programs have demonstrated efficacy in reducing delirium incidence (Inouye, 2000; Inouye, Bogardus, Baker, Leo-Summers, & Cooney, 2000; Inouye, et al., 1999; Marcantonio, et al., 2001), but the overall evidence base is underdeveloped (Fick, et al., 2002). The following review will present the evidence regarding cognitive stimulation interventions as well as interventions for delirium.

Cognitive Stimulation for Dementia

The accumulated empirical evidence supporting the benefits of cognitive stimulation interventions for people with dementia led to the United Kingdom's National Institute for Health and Clinical Excellence (NICE) and the Social Care Institute for Excellence (SCIE) joint recommendation that cognitive stimulation programs be used routinely in the treatment of mild or moderate dementia (NICE-

SCIE, 2011). A recent Cochrane Review concluded that cognitive stimulation provides cognitive benefits beyond medication alone, and these benefits may be maintained for a year or longer (Woods, et al., 2012). Cognitive stimulation programs have demonstrated cognitive function benefits comparable to pharmacologic therapies, improvements in quality of life, and cost-effectiveness (Spector, et al., 2008).

Aguirre et al. (2013) conducted a systematic review and meta-analysis to evaluate the effectiveness of cognitive stimulation trials in dementia. Studies included were RCTs testing a cognitive stimulation intervention, as defined by Clare and Woods (2004), involving a group or family caregiver, for individuals with a diagnosis of dementia, and including an evaluation of at least one cognitive measure. Data from fifteen studies (718 subjects) were ultimately included in the analyses. The results demonstrated a consistent significant benefit to cognitive function as a result of cognitive stimulation, but also benefits to self-rated well-being and quality of life. Overall, the cognitive stimulation interventions indicated improvement in cognitive function (effect size=0.41(0.25-0.57)) as well as communication and social interaction (effect size=0.44(0.17-0.71)). No clear relationship was found between the amount, frequency, or duration of the intervention and the outcomes; the necessary dose for such interventions to maximize benefits is yet unknown.

A systematic review and meta-analysis of non-pharmacological therapies in AD evaluated the effectiveness of cognition-focused interventions, including cognitive stimulation (Olazarán, et al., 2010). Included studies were randomized controlled trials (RCTs) published in a peer-reviewed journal that utilized participants with cognitive impairment or dementia, tested the efficacy of a non-pharmacological intervention, and implemented appropriate statistical analyses. A total of 179 RCTs were included in the analysis, 10 of which were identified as cognitive stimulation interventions for persons with dementia. Group sessions of cognitive stimulation indicated improvements in cognition (effect size=0.442(0.197-0.688)) in attention and memory (Bach, Bach, Bohmer, Fruhwald, & Grilc, 1995; Woods, 1979), orientation and language (Gerber, et al., 1991), and general cognition (Breuil, et al., 1994;

Spector, et al., 2003). The addition of multiple components to group cognitive stimulation, such as relaxation therapy, indicated improvement in general cognition (effect size=0.307(0.036-0.578); S. B. Chapman, Weiner, Rackley, Hynan, & Zientz, 2004; Meguro, et al., 2008; Olazarán, 2004; Poon, Hui, Dai, Kwok, & Woo, 2005; Tadaka & Kanagawa, 2004). Pooling of group cognitive stimulation RCTs yielded the highest effect (effect size=0.608(0.092-1.124)) on behavior in institutionalized persons with dementia (Baines, Saxby, & Ehlert, 1987; Gerber, et al., 1991; Robichaud, Hebert, & Desrosiers, 1994). Overall, a Grade B treatment recommendation was made for the ability of cognition-focused interventions, including cognitive stimulation, to improve cognition and behavior among persons with dementia.

Group cognitive stimulation therapy. Cognitive stimulation has been extensively evaluated by a group of researchers in the United Kingdom using a consistent approach to therapy: 14 themed activities delivered in bi-weekly group sessions of 45 minutes each (Spector, et al., 2003). The program was designed to provide global cognitive stimulation in an implicit way, emphasizing cognitive processing rather than correct answers, in a multisensory approach with integrated elements of reminiscence. Each session focuses on a theme such as childhood, food, or famous faces and begins with a non-cognitive physical warm-up activity to provide continuity and orientation to the group. The cognitive portion of the session includes group discussion on the theme of the day with an emphasis on multi-sensory stimulation. Reminiscence is included as is natural to the topic. Activities are modified to match the group's cognitive capacities, interests, and gender mix. Information processing rather than factual knowledge is emphasized (Spector, Orrell, Davies, & Woods, 2001). Beginning in 2003, the first RCT of this approach to cognitive stimulation was published (Spector, et al., 2003), to be followed by additional extensions of this research including investigating effects on specific areas of cognitive function (Spector, et al., 2010) as well as an lengthening of the intervention with maintenance cognitive stimulation therapy (Aguirre, et al., 2010). The following summary will critically analyze this body of evidence.

The first large-scale, multi-center RCT of this group approach to cognitive stimulation therapy (CST) included 201 participants with mild to moderate dementia from 23 adult day centers and residential facilities (Spector, et al., 2003). The treatment group (n=115) received 14 sessions of CST over seven weeks; the control group (n=86) received usual care. Outcome measures were change in cognitive function as measured by the Mini-mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) and the Alzheimer's Disease Assessment Scale – Cognition (ADAS-Cog; Rosen, Mohs, & Davis, 1984) and quality of life as measured by the Quality of Life – Alzheimer's Disease scale (QOL-AD; Logsdon, Gibbons, McCurry, & Teri, 2002), all with established validity and reliability. An intention to treat analysis was employed and statistical analysis controlled for baseline scores on outcome measures as well as demographic characteristics. Statistically significant differences were found between groups on all outcome measures such that the CST group scored higher on the MMSE (1.14(.09), $p=.044$) and ADAS-Cog (2.37(.87), $p=.006$) after treatment and rated their quality of life higher (1.64(.78), $p=.01$) than the control group. The promising results in this study led to further examination of this particular approach to cognitive stimulation and an attempt to determine the precise areas of cognition that may be affected as well as the possibility of maintaining long-term benefits.

The Spector et al. (2003) study was extended for a group of 35 participants in order to explore the effects of a maintenance program of CST (Orrell, Spector, Thorgrimsen, & Woods, 2005). Four of the original 23 facilities agreed to participate, two in the maintenance trial and two as comparison facilities. Participants were placed into three groups: eight participating in both the original CST as well as the maintenance CST groups, 12 in a CST only group, and 15 who received no CST. Maintenance CST consisted of 16 weekly maintenance sessions that followed the same protocol as the previously described CST. The same instruments were used to measure cognitive function and quality of life, and additional assessments of communication and behavior were added. MMSE scores improved for maintenance CST over the study period, but declined overall for both comparison groups ($p=.012$).

While MMSE scores for the CST only group improved by 1.09 during active treatment, scores declined during the follow-up period and were ultimately 1.95 points, on average, lower than baseline indicating that the benefits were not maintained. The maintenance CST group improved MMSE scores by an average of 1.25 during CST and continued to improve scores by another 0.62 points during the extended treatment. There were no significant improvements in quality of life, communication, or behavioral function following CST, including in those receiving maintenance CST. This study was a pilot study with a small sample, and therefore results should be interpreted with caution. There may have been insufficient power to detect differences between the groups in other outcomes. Overall, these results do show the potential benefit of maintenance cognitive stimulation in retaining gains made during CST. Following the positive results of this pilot study, a full scale, multi-center RCT of maintenance CST is currently underway (Aguirre, et al., 2010)

The specific benefits of CST were further explored with a secondary analysis of study data from the original RCT (Spector, et al., 2010). This study examined the specific subscales of the ADAS-Cog to determine whether some domains of cognition are distinctively affected by CST. These areas included memory and new learning, praxis, and language. As reported in the parent study (Spector, et al., 2003), there was a significant difference between treatment and control groups on the ADAS-Cog total score after completion of the CST program; however, the secondary analysis showed that improvement only occurred in the language subscale (Spector, et al., 2010). This may be due to the group approach to cognitive stimulation that was used, in which verbal communication is a core component rather than learning or rehearsal of specific information. It is not possible to determine whether the social nature of the groups themselves contributed to improvement in communication performance, or whether it was the specific components of the cognitive stimulation protocol (Spector, et al., 2008).

Individualized cognitive stimulation. The potential for individualized cognitive stimulation to improve outcomes for people experiencing cognitive decline has not been fully explored, although it has

been identified that there is a need for this approach to intervention (Spector, et al., 2008). It is acknowledged that some people may not be good candidates for a group intervention due to personal preferences, lack of access, or functional limitations. One study has compared individualized cognitive stimulation to other individualized interventions for people with dementia implemented by caregivers (Quayhagen, et al., 2000). Caregivers (n=103) and their dementia-diagnosed spouses were randomized to one of four treatment programs or a wait-list control group: cognitive stimulation, dyadic counseling, dual supportive seminar, or early-stage day care. Cognition-related outcomes (memory, verbal fluency, and problem-solving ability) were assessed at baseline and following a three month intervention period. Individualized cognitive stimulation demonstrated more improvement in cognition-related outcomes compared to the other treatment groups. Similar findings were also reported in an RCT that utilized caregivers to deliver a dementia intervention that included aspects of cognitive stimulation (Onder, et al., 2005). Further development of individualized cognitive stimulation interventions is needed to develop the evidence base regarding their effectiveness.

In summary, cognitive stimulation is a generalized approach to cognition-focused intervention. It may be conducted in a group or individualized format, although the majority of the evidence for its benefit is in relation to the group cognitive stimulation therapy approach. Limitations of the group approach include the inability to distinguish specific cognitive benefits from social improvements. Indeed, language function appears to be the more affected by this approach. A limited body of evidence has explored the potential of individualized cognitive stimulation and demonstrated cognition-specific benefits. A need for further research has been identified, specifically regarding individualized interventions, although there is a substantial body of evidence to support the potential of cognitive stimulation broadly to improve outcomes for individuals with dementia.

Interventions for Delirium

Broad treatment goals for delirium include identifying potential causes and eliminating them, providing supportive care, preventing complications, and treating behavioral symptoms (Inouye, 2006), but specific strategies for intervention are lacking, particularly when the underlying cause cannot be determined or is not modifiable. Prevention of delirium is the most effective approach for avoiding negative consequences and most research has focused on this approach. The National Institute for Health and Clinical Excellence (NICE) developed a guideline for the prevention of delirium based on the accumulated evidence (O'Mahony, Murthy, Akunne, & Young, 2011). It includes detailed recommendations such as utilizing a multi-disciplinary team trained and competent in delirium prevention, introducing cognitively stimulating activities, addressing physical needs such as hydration status and optimal oxygen saturation, and conducting a thorough medication review. The NICE-developed guidelines for management of incident delirium, however, are much broader: identify and manage the possible underlying causes; ensure effective communication and reorientation and provide reassurance; and, provide a suitable care environment consistent with the principles of delirium prevention (Young, et al., 2010). The lack of empirically-validated intervention protocols to treat delirium is a notable gap in the scientific literature.

Pharmacological treatment of delirium. Cholinergic deficiency is the leading hypothesis regarding the mechanism of delirium (Hshieh, et al., 2008) and the death of cholinergic neurons is known to result in an acetylcholine deficit with accompanying cognitive impairment in Alzheimer's disease (Heininger, 2000; Herholz, Weisenbach, & Kalbe, 2008) and other dementias (Korczyn & Reichmann, 2006; J. Wang, Zhang, & Tang, 2009). Therefore, the cholinergic deficiency hypothesis is the most pertinent to a discussion regarding current pharmacological treatment of delirium in the presence of dementia.

Acetylcholinesterase inhibitors (AChEIs; e.g., donepezil, rivastigmine) increase cholinergic activity by inhibiting the anti-cholinergic activity of acetylcholinesterase and have demonstrated statistically significant improvements in cognition among individuals with dementia (Qaseem, et al., 2008), although the clinical significance of these improvements is still debated. Non-pharmacological approaches are considered first-line treatment for delirium and medications are generally not recommended (Fong, Tulebaev, et al., 2009); however, AChEIs have been investigated for their effectiveness in improving or resolving delirium.

A 2009 systematic review of randomized controlled trials identified 13 studies that evaluated antipsychotics (primarily), AChEIs, an antiepileptic, an anesthetic, a sedative, and a benzodiazepine in delirium treatment or prevention (Campbell, 2009). Among the three trials identified which tested an AChEI or precursor, none demonstrated an impact on delirium symptoms. A Cochrane systematic review (Overshott, Karim, & Burns, 2008) found only one randomized controlled trial (Liptzin, Laki, Garb, Fingerroth, & Krushell, 2005) that investigated an AChEI (donepezil) in the prevention of delirium which lacked sufficient power to detect a difference between groups. While other case reports were found which describe the efficacy of the AChEI rivastigmine, the review concluded that there was no current evidence to support the efficacy of AChEIs in the treatment of delirium.

Additional studies since the Cochrane review have investigated the use of rivastigmine on delirium. A pilot study within an epidemiological study investigated the use of rivastigmine as treatment for stroke patients (n=17) with severe and persistent delirium (Oldenbeuving, de Kort, Jansen, Kappelle, & Roks, 2008). All but one of the patients exhibited a significant decrease in delirium severity after treatment and no major side effects were reported. However, the lack of control group and small sample size were notable study limitations. More recently, a double-blind, randomized, placebo-controlled trial of rivastigmine for the *prevention* of postoperative delirium in older cardiac surgery patients was conducted (Gamberini, et al., 2009). Participants (n=120) aged 65 or older undergoing

elective cardiac surgery were randomly assigned to receive placebo or rivastigmine prior to surgery and until the sixth postoperative day. No significant differences were found between the groups in any of the outcomes measured including delirium incidence, delirium duration, number of patients receiving haloperidol or lorazepam (typical delirium treatment at the study location when physicians diagnosed delirium), or length of hospital stay. Overall, the study did not support the use of short-term prophylactic use of rivastigmine to prevent postoperative delirium in this population.

Most recently, a double-blind, placebo-controlled randomized trial was conducted which investigated whether the addition of rivastigmine to usual care for critically ill patients would reduce the duration of delirium (van Eijk, et al., 2010). Participants (n=104) aged 18 years or older diagnosed with delirium were enrolled from six intensive care units over an approximately two year period and randomized to receive rivastigmine or placebo in conjunction with the typically prescribed haloperidol. Delirium was assessed daily using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). No statistically significant differences were found between the groups in delirium duration (the primary outcome). Furthermore, the rivastigmine group demonstrated significantly higher delirium severity, longer stay in the ICU, and higher mortality than the placebo group. Due to the higher mortality among those in the treatment group, the study was halted after enrollment of the first 104 subjects (Skrobik, 2010). The study concluded that rivastigmine not be recommended in the treatment of delirium in critically ill patients.

Although the overall body of scientific evidence does not support the use of rivastigmine in the treatment of delirium, one study of its use in delirium in vascular dementia did demonstrate evidence of benefit (Moretti, Torre, Antonello, Cattaruzza, & Cazzato, 2004). Participants (n=246) were ambulatory outpatients aged 65 to 80 with a diagnosis of probable vascular dementia, subcortical vascular dementia, or multi-infarct dementia. Two age- and education-matched groups were utilized rather than randomly assigned groups; one received rivastigmine while the other received aspirin. Caregivers

notified the research staff if any changes in status of the participant occurred, including behavioral or cognitive changes, upon which the CAM was administered. Participants were followed for 24 months. The rivastigmine group presented with significantly fewer episodes of delirium during the study period as well as shorter delirium duration upon presentation. Although these findings provided preliminary evidence of the benefit of rivastigmine for delirium among persons with vascular dementia, no additional or better-controlled studies were identified.

The current National Institute for Health and Clinical Excellence (NICE) guidelines recommend that first-line delirium treatment include identification and management of underlying cause(s) as well as communication, reorientation, and reassurance (i.e., non-pharmacological approaches; (NICE, 2010)). According to these guidelines, pharmacological treatment is reserved for short-term treatment with haloperidol or olanzapine (antipsychotics) and only in certain cases. Although this conclusion has been criticized as an oversimplification of the value of pharmacological treatment in delirium (T. A. Tahir, 2011), this criticism has been directed at the guidelines regarding antipsychotics rather than the lack of inclusion of AChEIs. Medications including olanzapine (Skrobik, Bergeron, Dumont, & Gottfried, 2004) and haloperidol (Bookbinder & McHugh, 2010) have demonstrated some efficacy in reducing delirium symptoms. However, an RCT of quetiapine, an antipsychotic, as a treatment for delirium was ended prematurely based on Food and Drug Administration concerns that the medication may be inappropriate for use in an older adult population (T. Tahir, et al., 2010). Based on current evidence, the use of pharmacological treatments should be considered with extreme caution, at low doses, and for short periods of time only (Young, et al., 2010).

Non-pharmacological treatment of delirium. Non-pharmacological intervention programs for individuals with delirium are preferred but have not been tested to the same extent as pharmacological approaches. Flaherty (2011) provided a summary of key components of studies which jointly targeted the prevention and management of delirium. These included staff education, systematic screening for

delirium, use of multiple disciplines, use of multiple components, use of geriatric principles, and a focus on non-pharmacological interventions. Overall, non-pharmacological approaches tend to include the following elements: assisting orientation, promoting sensory function, healthy sleep-wake cycles, pain relief, optimizing hydration and electrolytes, mobilization, and active review by members of a geriatric team (O'Hanlon, et al., 2013). However, many interventions are commonly suggested without empirical support (Rapp, Mentis, & Titler, 2001).

A review of interventions to treat delirium found only one RCT that implemented a non-pharmacological intervention in delirious older adult patients (Weber, et al., 2004). This study by Cole et al. (2002) used an intervention consisting of a consultation by a geriatric specialist to determine potentially precipitating and perpetuating factors of delirium as well as recommendations for treatment and subsequent follow-up by the consultant and a nurse. The study sample included 227 patients aged 65 or older admitted to five general medical units with delirium and randomized to intervention or usual care groups. Multiple assessments were made to track cognitive status including three assessments during the first week of admission and weekly assessments for up to eight weeks or until discharge. Multiple outcomes were measured with well-established instruments for mental status, delirium severity, physical function as well as length of stay, rate of discharge, discharge disposition, and survival. Although the study methodology was rigorous, there were no significant differences between the treatment and control groups during the eight week study period. The strong study design controlled for many extraneous factors that could potentially influence outcomes; therefore, the intervention itself may have been ineffective.

A second systematic review conducted in 2004 explored the efficacy of multi-component intervention strategies for delirium in hospitalized older adults and included a broader range of methodologies (Milisen, et al., 2005). Although preventative interventions demonstrated some success across studies, treatments for existing delirium had mixed outcomes. Only one identified study

demonstrated effectiveness in delirium treatment, a study that tested a nurse-led interdisciplinary intervention program to reduce the incidence, severity, and duration of delirium among older adults with hip fractures (Milisen, et al., 2001). A sequential before/after design was used in which 60 patients were first enrolled in the non-intervention cohort, followed by 60 patients enrolled in the intervention cohort approximately six months later. A modified version of the Confusion Assessment Method (CAM; Inouye, et al., 1990) was used to assess delirium incidence as well as severity. Intervention components included: educating nursing staff regarding delirium; implementing systematic cognitive screening; utilizing consulting services of a delirium resource nurse, a geriatric nurse specialist, or a psychogeriatrician; and, use of a scheduled pain protocol. Among intervention group participants who developed delirium, it was, on average, less severe ($p=.0152$) and of shorter duration (median = 1 day in intervention cohort, median = 4 days in non-intervention cohort, $p=.03$) than in non-intervention group participants who developed delirium.

The Hospital Elder Life Program (HELP) was designed to prevent functional and cognitive decline in older adults during hospitalization, including delirium (Inouye, et al., 2000). All patients age 70 or older on specified units are screened for six delirium risk factors: cognitive impairment, sleep deprivation, immobility, vision impairment, hearing impairment, and dehydration. An interdisciplinary team including a geriatric nurse specialist, specially trained Elder Life Specialists, and trained volunteers implements interventions which are targeted to the risk factors identified during the screening. Core intervention components include a daily visitor to assist in orientation, cognitively stimulating activities three times per day, early mobilization, vision and hearing protocols, feeding and fluid assistance, and a non-pharmacologic sleep protocol. In a controlled study of 852 patients 70 years of age or older, the HELP program group demonstrated a lower rate of delirium development, total number of days with delirium, and total number of delirium episodes (Inouye, et al., 1999). Although the nature of the intervention, which utilizes multiple components simultaneously, prohibits the ability to identify the

strength of individual factors contributing to the positive outcomes demonstrated, these findings suggest that an intervention protocol which includes cognitively stimulating activities may be effective in reducing delirium incidence and length. HELP was recently adapted for use in a community hospital (Zaubler, et al., 2013). Delirium rate, length of stay, and healthcare costs were assessed in 595 patients ages 70 or older admitted to a general medical floor. Assessments were taken during a four month pre-intervention period and compared to assessments during a nine month intervention period. Following the HELP intervention, delirium episodes decreased by 40% ($p=.019$), length of stay decreased by two days ($p<.001$), and the intervention resulted in \$841,000 in cost savings during the nine month period.

In summary, the evidence regarding intervention effectiveness in people with delirium is limited but growing. The possible benefit of pharmacological management has yet to be demonstrated and may actually lead to poorer outcomes. Non-pharmacological methods are preferred, but most interventions target delirium prevention rather than treatment. Few studies have explored treatment of an existing delirium and those available were largely ineffective. Not only is additional research recommended, but research that specifically considers the influence of staff adherence to treatment protocols as well as underlying causal mechanisms of delirium has been recommended (Milisen, et al., 2005). Furthermore, attempts to improve cognitive function directly in people with delirium are absent in the literature. This approach has been utilized successfully with cognition-focused interventions in individuals with dementia. Considering the close relationship between dementia and delirium, intervention approaches that demonstrate success in improving cognitive functioning in dementia may hold similar promise for delirium treatment.

Interventions for Delirium in Individuals with Dementia

In practice, the treatment of delirium in individuals with dementia is the same as recommended treatment in individuals without dementia: identification and management of potential causes including medications, infection, dehydration, electrolyte imbalance, sensory deprivation, intracranial symptoms,

urinary or fecal difficulties, myocardial or pulmonary problems, and hypo- or hyperglycemia (Flanagan & Fick, 2010). However, therapeutic interventions that target the resolution of delirium among persons with dementia in the absence of identifiable causes, or in conjunction with such management, have only recently been explored. A 2000 Cochrane review aimed to assess the evidence regarding the effectiveness of multi-disciplinary team interventions in the care of individuals with delirium who had an underlying chronic cognitive impairment (Britton & Russell, 2000). The authors found no studies which focused on patients with prior cognitive impairment; therefore, management of delirium in this group could not be assessed.

A recent pilot study of a cognitively stimulating activity intervention for people with dementia who developed delirium during hospitalization demonstrated improvement in delirium prevalence, severity, and attention in the intervention group compared to the control group (Kolanowski, Fick, Clare, Steis, et al., 2010). This research continues within Recreational Stimulation for Elders as a Vehicle to resolve DSD (RESERVE-DSD; Kolanowski, Fick, Clare, Therrien, et al., 2010), the parent study of this investigation.

Summary: Interventions for Dementia and Delirium

Preliminary evidence suggests that a cognition-focused intervention may improve cognitive functioning in individuals with dementia who develop delirium. Among individuals with dementia alone, cognitive stimulation interventions have demonstrated the ability to improve general cognition, attention, memory, and language. Individualization of these approaches may offer additional benefits.

Personality and Cognitive Decline

Personality is best described based on three key points: it is an intrinsic structure of an individual's world that allows self-organization and orientation to the world; it is stable over time such that individuals remain relatively consistent throughout life; and, although behavior may change, the individual maintains consistency in different contexts (Piedmont, 1998). Personality is stable as well as

dynamic, influenced by culture, context, and situation throughout one's lifetime and responsive to both internal and external demands. Personality traits are individual differences between people, "the relatively enduring patterns of thoughts, feelings, and behaviors that distinguish individuals from one another" (Roberts & Mroczek, 2008, p. 31).

Multiple theories have been proposed to describe the structure of personality, or the explanatory constructs of individual behavior and motivation (Ewen, 2010). The predominant framework for the study of personality characteristics in scientific research is the Five Factor Model. Furthermore, it is considered both consistent and appropriate for studies of personality and health (Timothy Smith & Williams, 1992). The Five Factor Model guided this investigation of the moderating effects of personality on treatment outcome.

The Five Factor Model of Personality

The Five Factor Model evolved from the historical emergence of the "Big Five" factors of personality (Wiggins, 2003). The development of a factor approach to the study of personality began with Cattell (1933, 1943, 1966) who sought to determine the behaviors encompassed by personality through identification and reduction of "surface" personality traits by factor analysis to their underlying "source" traits. This work was enhanced by Thurstone (1934) and Allport & Odbert (1936) who undertook exhaustive studies of trait-descriptive adjectives which determined broad categories, or clusters, of traits through factor analysis. An impressive body of research followed, during which a taxonomy of personality attributes was developed and refined, leading to the "Big Five" taxonomy of personality factors (Wiggins, 2003). Among researchers, factor names differed slightly (such as agreeableness versus likeability), but the science evolved to agree on five broad personality domains, or traits, within the framework: *neuroticism*, *extraversion*, *openness to experience*, *agreeableness*, and *conscientiousness* (Costa, 1991; Wiggins, 2003).

Neuroticism. *Neuroticism* is described as the chronic experience of distressing emotions (McCrae, 1991). Its assessment provides a view of affective adjustment in less neurotic individuals versus emotional instability in highly neurotic individuals (Piedmont, 1998). High scores include susceptibility to psychological distress including agitation, depression, irrational ideas, hostility, and tendency for negative affect, as well as difficulty controlling impulses and poor reactions to stress (McCrae & Costa, 2010). Low neuroticism scores indicate emotional stability, relaxed personality, and a lack of defensiveness.

Extraversion. *Extraversion* assesses two qualities: interpersonal involvement and energy (Piedmont, 1998). These represent an individual's preferences for the quantity and quality of interpersonal interactions, level of activity, and capacity for joy. High scores indicate sociability, friendliness, open attitude, talkativeness, assertiveness, as well as a preference for stimulation and excitement (McCrae & Costa, 2010). Low extraversion scores reflect reserved, less assertive, and less active personalities. Introversion is considered the absence of extraversion rather than its opposite.

Openness to Experience. *Openness to experience* refers to an individual's preference for actively seeking experience as well as appreciation of experience in general (Piedmont, 1998). It includes aesthetic sensitivity, attentiveness to inner feelings, preference for variety, active imagination, independent judgment, and intellectual curiosity (McCrae & Costa, 2010). Open individuals are curious, untraditional, and creative individuals. Low openness scores indicate individuals who prefer the familiar to the novel, are more conventional and pragmatic, and tend to display muted emotional responses.

Agreeableness. *Agreeableness* describes an individual's attitudes toward others, their tendency toward cooperation or competition within interactions (Piedmont, 1998). It is a dimension of altruistic behavior (Costa, McCrae, PsyPro Corporation, & PAR Staff, 2010). Agreeable individuals are compassionate, trusting, forgiving individuals. They are eager to help, cooperative, willing to consider others' solutions, and tend to be more popular. Those who are not agreeable are frequently

antagonistic, manipulative, vengeful, egocentric, skeptical, and competitive. They tend to be less modest and less straightforward.

Conscientiousness. The final domain, *conscientiousness*, assesses goal-directed behavior. Specifically, the degree of organization, persistence, and motivation an individual possesses (Piedmont, 1998). Conscientious individuals are dependable, purposeful, reliable, self-disciplined, determined, strong-willed people (McCrae & Costa, 2010). Low conscientiousness scores reflect a hedonistic personality lacking order and lackadaisical or unreliable behavior. These individuals are often described as unreliable, negligent, and aimless.

Advantages of the Five Factor Model. The Five Factor Model summarizes individual differences in emotional, interpersonal, experiential, attitudinal, and motivational styles (McCrae, 1991). It is highly applicable to both research and practice endeavors because it has been operationalized into instruments that may be used across studies, settings, and populations (McCrae & John, 1992). Three specific advantages of the Five Factor Model include its integration of multiple personality constructs providing for investigation of specific traits of interest, the comprehensiveness of the model allowing for exploration of the interaction of personality traits within individuals, and the efficiency of the approach which provides a global view of personality with five overall domain scores. It additionally offers two distinct advantages within health research: thorough instruments have been developed based on the strong theoretical base of five factor theory; and, these instruments have been well-tested and their validity is demonstrated and accepted (Timothy Smith & Williams, 1992). Utilizing valid multi-trait measurements of personality is a vital component of high quality personality and health research (Kern & Friedman, 2011).

Personality Stability in Aging

Personality *stability* refers to the tendency for personality to both increase in consistency throughout life as well as reach a relative plateau in adulthood (Caspi & Roberts, 2001). It has been

consistently stated that after age 30, there is little change to the underlying, internal structure of personality although adaptation to the environment continues to occur within that stable structure (Costa & McCrae, 2006; McCrae & Costa, 1996; Piedmont, 1998; Terracciano, et al., 2006; Terracciano, et al., 2010). However, a static view of stability, or the position that personality does not change throughout adulthood, has been directly criticized and contested (e.g., Roberts, Walton, & Viechtbauer, 2006b). Alternatively, the more dynamic view of personality stability does not advocate complete rigidity, but rather an overall continuity in personality in adulthood with relatively modest changes (Costa & McCrae, 2006). Although debate continues regarding what constitutes continuity of personality in adulthood, the preponderance of the scientific evidence supports general consistency of personality profiles throughout the aging process (Fraley & Roberts, 2005; Roberts & DelVecchio, 2000).

The consistency of personality traits over time is typically investigated as either mean-level or rank-order consistency. Mean-level consistency refers to the increase or decrease on trait dimensions such that if personality traits of groups change reliably over time, personality is considered inconsistent (Roberts & DelVecchio, 2000). Alternatively, rank-order consistency refers to the personality traits of individuals in relation to their group. Groups of people who retain the same rank ordering of personality traits over time are considered to demonstrate rank-order stability. Both mean-level and rank-order consistency are important considerations when viewing the stability of personality over time.

The substantial body of evidence describing these phenomena has been investigated through comprehensive meta-analysis (Roberts & DelVecchio, 2000; Roberts, Walton, & Viechtbauer, 2006a). In a meta-analysis of 92 longitudinal studies of personality change over time, Roberts, Walton, & Viechtbauer examined the mean-level changes of the “Big Five” personality traits over the life course (2006a). Rigorous criteria for study inclusion were implemented including: measurement of trait variables rather than attitudes or temperament; test-retest intervals of greater than or equal to one year; information on mean-level change, sample size, and age; non-clinical sample; and, homogeneous

age samples to ensure that the effect of age on development could be investigated. The included studies provided data on 50,120 participants and 1,682 estimates of change. Their findings support a pattern of normative change in personality traits across the life course with the highest degree of mean-level change occurring during young adulthood and less change during late life. Significant findings during later adulthood include a decrease in social vitality (a facet of extraversion) during the age 60 to 70 period ($d = -.16, p < .05$), an increase in agreeableness between the ages of 50 and 60 ($d = .30, p < .05$), an increase in conscientiousness from age 60 to 70 ($d = .22, p < .05$), and a decrease in openness to experience between the ages of 60 to 70 ($d = -.19, p < .05$). The study findings show strong evidence of mean-level personality trait change after age 30, including some change during older age, although changes were small in magnitude. Personality change was most prominent during young adulthood (age 20 to 40), with little change occurring in old age.

Rank-order stability was similarly investigated in a meta-analysis of 152 longitudinal studies (Roberts & DelVecchio, 2000). Along with the Big Five taxonomy of personality traits, measures of temperament were also included and categorized into seven dimensions. Inclusion criteria were similar to the mean-level change meta-analysis including: measurement of trait or temperament variables rather than attitudes or values; test-retest intervals of greater than one year; information on test-retest interval, sample size, and age; and, non-clinical sample. The final sample included 55,180 participants and 3,217 rank-order consistency coefficients. Trait consistency was found to increase from a test-retest correlation coefficient of .31 during childhood to .54 during the college years, and to .64 at age 30. Between ages 50 and 70, trait consistency reached a plateau of approximately .74. Measurements after age 73 were not included in the data. The peak of trait consistency occurred during the ages of 50 to 59 and remained high during the following years, although the rank-order consistency of personality traits after this peak does not preclude some level of personality trait change in late adulthood.

The results of these two meta-analyses provide a relatively comprehensive view of personality stability over the life course, including during old age. While rank-order stability progressively increases with age and plateaus in old age, mean-level change demonstrates some significant differences in select traits after age 50, although changes are generally small. Taken together, these results suggest that over time, people become more consistent in their relationship to one another (i.e., those who are high in one personality trait will remain high in that trait compared to others), this level of consistency is stable in old age, with mean-level changes occurring primarily in young adulthood, and isolated mean-level changes in late life may occur but are not normative. Therefore, particularly among older adults, personality stability is supported among both mean-level and rank-order consistency literatures. Overall continuity of personality in late adulthood with relatively modest changes (Costa & McCrae, 2006) is a description of stability consistent with empirical evidence.

Personality Stability in Dementia

Although personality traits are considered largely stable throughout the life course, significant personality change has been associated with the onset and progression of dementia, to the extent that it may be considered diagnostic (e.g., Aussen, Edman, Almkvist, & Bogdanovic, 2009; Balsis, Carpenter, & Storandt, 2005). However, *personality stability during the early stages of the dementia trajectory* has been demonstrated according to the dynamic view of stability previously described: individuals maintain rank-order consistency with relatively modest mean-level changes (Chatterjee, et al., 1992; Dawson, et al., 2000; Strauss & Pasupathi, 1994; Twigg, Burgener, & Popovich, 2007). *Premorbid personality* refers to the personality profile of an individual with dementia prior to the development of dementia-related symptoms. Empirical evidence supports the view that personality in early-stage dementia is very similar to premorbid personality, particularly in regard to rank-order stability of traits.

Personality change as indication of dementia onset. Changes in personality are accepted diagnostic features of frontotemporal dementia (Neary, et al., 1998), and have been reported as

preclinical AD symptoms (Balsis, et al., 2005; Smith-Gamble, et al., 2002). However, since behavioral symptoms demonstrate weak sensitivity and specificity as early diagnostic features of AD, they are typically considered as supportive evidence only in later stages of disease (Dubois, et al., 2007). The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Revised lists personality change as an associated feature of dementia rather than a diagnostic criterion (American Psychiatric Association, 2000).

Among individuals with subjective cognitive impairment (SCI) and mild cognitive impairment (MCI), conditions which may represent preclinical stages of AD (Reisberg & Gauthier, 2008), one study demonstrated specific patterns of self-reported personality alterations in the SCI (n=24) and MCI (n=35) groups compared to healthy controls (n=26; Aussen, et al., 2009). Participants with SCI and MCI had higher scores in traits related to anxiety proneness ($p < .001$) and aggression-hostility ($p = .042, .039$) as well as lower scores in aspects of extraversion ($p = .033, .036$). A comprehensive inventory based on the Five Factor Model was not used. Although these findings may indicate personality trait changes due to preclinical AD pathology, the heterogeneity of individuals with SCI and MCI precludes the ability to draw conclusions. While the diagnosis of MCI is associated with an increased risk of dementia (DeCarli, 2003), up to two thirds of those diagnosed with MCI have been shown to remain cognitively stable after three years (Wahlund, Pihlstrand, & Jonhagen, 2003).

Examination of personality changes as indicators of dementia onset have been investigated in additional studies; however, formal measures of personality assessment were not implemented. In a study by Balsis, Carpenter, & Storandt (2005), longitudinal data from 108 individuals over a 22 year period were used; no participants had dementia at recruitment and 68 received a clinical dementia diagnosis during the study period. Items from the Blessed Dementia Scale (Blessed, Tomlinson, & Roth, 1968) were used as indicators of personality change based on informant report. These included increased rigidity, increased egocentricity, loss of concern for feelings of others, coarsening of affect,

impaired emotional control, diminished emotional responsiveness, growing apathy, and purposeless hyperactivity. In 47% of individuals who ultimately were diagnosed with dementia, personality change occurred prior to diagnosis. Most commonly, these changes were increased rigidity (25%) and growing apathy (24%). In comparison, 23% of non-demented individuals demonstrated any personality change.

In another study, 3,021 subjects participated in a longitudinal, population-based survey of African Americans and Nigerians and were followed for dementia diagnosis over a two year period (Smith-Gamble, et al., 2002). Among these, incident dementia cases occurred in 45 subjects. Informants provided information on personality change and dementia status. Personality change was measured using questions from The Cambridge Examination for Mental Disorders of the Elderly (CAMDEX): Have you noticed any changes in his/her personality?; Has he/she become more irritable?; Has he/she become more stubborn?; Does he/she show less concern for other people?; Is there a loss of interest or enjoyment in things in general?; and, Has he/she lost interest in things he/she used to enjoy? (Roth, Tym, & Mountjoy, 1986). A change in personality, quantified as an affirmative answer to any of the previous questions, was found to be a significant predictor of dementia after adjusting for cognition and functional status. On average, personality change was reported two years prior to dementia diagnosis.

In both the Balsis, Carpenter, & Storandt and Smith-Gamble et al. studies, personality measures were not taken from established personality assessment tools but rather from items in dementia screening inventories. The lack of measurement based on established personality measures or based on solid personality theory is a notable limitation. Furthermore, the questions utilized from these inventories are almost exclusively related to non-cognitive symptoms of dementia such as apathy. These behavioral and psychological symptoms could be interpreted as changes in personality by informants, but may be more appropriately attributed to manifestations of underlying dementia pathology (Kitwood, 1997; Twigg, et al., 2007; von Gunten, Pocnet, & Rossier, 2009). Family members, for example, describe changes in the person with dementia based on behavior and report them as personality

changes when in fact they are due to disease-related pathology. Symptoms such as agitation and anxiety are alternatively viewed as attempts by the person with dementia to seek meaning, express or meet needs, and to cope with their world (Downs, Clare, & Anderson, 2008). Therefore, interpretation of such symptoms as personality change should be made with caution.

Normative personality changes in dementia and rank-order consistency. Although limited evidence supports the value of personality change as a diagnostic criterion for AD, a substantial literature has demonstrated personality change during the trajectory of dementia. Multiple studies of personality change in AD have demonstrated increases in neuroticism, decreases in extraversion, and decreases in conscientiousness with disease progression (Chatterjee, et al., 1992; Dawson, et al., 2000; Robins Wahlin & Byrne, 2011; Siegler, Dawson, & Welsh, 1994; Strauss & Pasupathi, 1994; Williams, Briggs, & Coleman, 1995). Some studies have also found decreases in openness to experience, although openness and agreeableness have generally been found to be relatively stable in dementia (Chatterjee, et al., 1992; Dawson, et al., 2000; Siegler, et al., 1994; Siegler, et al., 1991).

In a longitudinal study over 42 months, dementia progression and personality measures were collected at baseline and six month intervals (n=96; Twigg, et al., 2007). Baseline measures were taken within the first year of dementia diagnosis and a proxy rating of premorbid personality (five years prior to dementia onset) was also measured. Caregivers provided personality ratings using the Adult Personality Rating Scale (APRS; VanHaitma, Lawton, & Klapper, 1995) and the individuals with dementia provided self-ratings via the NEO-FFI (Costa & McCrae, 1992). Caregiver ratings indicated a change in the strength of certain personality traits over the early to middle disease stages: decreased extraversion ($p < .05$), decreased hostility ($p < .05$), decreased task-oriented ($p < .01$), and decreased neuroticism ($p < .05$). Significant differences between caregiver premorbid and baseline (within one year of dementia diagnosis) ratings were found for extraversion and task-oriented. Participant self-ratings of personality were more consistent, demonstrating stability in all traits except for extraversion which declined during

the 18 to 42 month period ($p < .001$). The authors noted that with disease progression, participants with dementia found it difficult to provide self-ratings of personality, particularly regarding certain items, leading to more neutral responses. Also, among proxy and self-ratings, the items which decreased reliability of ratings were found to be those that reflected disease-related changes (such as to what extent the family member enjoys housework or shows initiative) rather than true personality changes.

A systematic review of research that assessed personality change in AD included nine studies, all of which utilized well-accepted measures of the Five Factor Model of personality, the informant versions of the NEO-PI or NEO-FFI (Robins Wahlin & Byrne, 2011). The previously described study by Twigg et al. (2007) was not included. Across studies, participants were primarily diagnosed with AD, although some studies included cases of vascular dementia, mixed dementia, atypical dementia, or a broad descriptor of dementia. All personality scores were converted to T scores in order to compare sample scores to appropriate norms as is recommended for meaningful interpretation of the data. Effect sizes for the differences between premorbid and current personality trait scores were calculated across studies. Findings included systematic shifts from premorbid to current scores on multiple personality traits. Premorbid neuroticism scores increased from an average of 48.9 to 62.7 ($d = 1.18$), extraversion scores decreased from an average of 48.9 to 36.0 ($d = -1.21$), openness scores decreased from an average of 41.0 to 36.5 ($d = -0.49$), agreeableness scores decreased from an average of 50.0 to 47.0 ($d = -0.25$), and conscientiousness scores decreased from an average of 52.1 to 28.4 ($d = -2.17$). The highest degree of change was found for neuroticism, extraversion, and conscientiousness; conscientiousness demonstrated a marked decrease of between two to three standard deviation units across studies. These results indicate a consistent pattern of personality change (increased neuroticism, decreased extraversion, and decreased conscientiousness) with AD progression. However, it is not possible to determine the timing or degree of these changes throughout the dementia trajectory based on the review's findings. Studies included mean MMSE scores ranging from 15.3 to 22.2, indicating an average

level of cognitive impairment ranging from mild to moderate. The majority of studies reported mean MMSE scores of less than 20, indicating a moderate level of impairment of participants. Other studies have reported personality change during disease progression to be associated with severity of cognitive impairment (Aitken, Simpson, & Burns, 1999; Sollberger, et al., 2011).

Although changes in several personality traits may occur as dementia progresses, individuals tend to demonstrate rank-order consistency regarding their overall personality profile, particularly in the earlier stages (Kolanowski & Whall, 1996; Twigg, et al., 2007). For example, individuals who scored high on extraversion premorbidly remained high in that domain compared to others after the onset of AD (Dawson, et al., 2000; Strauss & Pasupathi, 1994). Rank-order consistency has been shown to be preserved following a dementia diagnosis in all traits except conscientiousness. In a study by Chatterjee et al. (1992), caregivers (n=38) of individuals with moderate dementia rated premorbid and current personality. Although mean-level changes were significant for all five personality traits, rank-order consistency of four traits was demonstrated. Significant correlations between premorbid and current personality ratings were found for neuroticism ($r=.76$), extraversion ($r=.67$), openness to experience ($r=.77$), and agreeableness ($r=.79$). Similar findings by Siegler et al. (1991) demonstrated mean-level change in neuroticism, extraversion, openness, and conscientiousness, but significant correlations between premorbid and current personality ratings, indicating rank-order consistency.

While personality change throughout the course of dementia has been relatively well-characterized, the association between these changes and cognition has only been recently explored. A recent study examined the influence of personality stability on cognitive performance at two time periods (1994-1995, 2004-2005) among community-dwelling adults (n=4,974) from the Midlife in the United States Study (E. K. Graham & Lachman, 2012). Findings demonstrated faster reaction times and better inductive reasoning among individuals who maintained stable neuroticism and openness to

experience scores. Personality stability in this case was associated with better cognitive performance; a consistent personality was more beneficial for cognitive functioning.

Cognitive Reserve and Personality

Personality traits affect behavior and preferences likely to influence activity participation and achievement during one's lifetime (McCrae & John, 1992; Wiggins, 1996) and therefore may influence cognitive reserve (Akbaraly, et al., 2009; Hall, et al., 2009; Nithianantharajah & Hannan, 2009; Vance, et al., 2010). An active lifestyle that includes a rich social environment was been associated with decreased dementia risk (Fratiglioni, Paillard-Borg, & Winblad, 2004; Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000; H. X. Wang, Karp, Winblad, & Fratiglioni, 2002). The development and maintenance of such a lifestyle is influenced by personality and therefore, personality may be a significant contributor to lifestyle preferences which impact cognitive reserve.

A systematic review of 12 longitudinal and three case-control studies was conducted to explore the association between personality and risk of dementia as well as MCI (L. F. Low, Harrison, & Lackersteen, 2013). Across studies, the authors concluded that higher neuroticism increased the risk for dementia while higher conscientiousness was protective. A small amount of inconsistent evidence demonstrated a potentially protective effect of increased openness. Neither extraversion nor agreeableness was associated with dementia risk. These results suggest that high neuroticism and low conscientiousness may negatively influence cognitive reserve capacity, thereby hastening the clinical manifestation of cognitive symptoms. The neurological changes associated with chronic stress and negative affectivity, common to high neuroticism, may lead to hippocampal atrophy (A. L. Lee, Ogle, & Sapolsky, 2002; Sapolsky, 2001). Alternatively, the healthier lifestyles common among those with higher conscientiousness (Bogg & Roberts, 2004) may provide brain-protective effects.

A recent study examined the link between personality traits and AD pathology directly. A cohort of individuals (n=111) participating in the Baltimore Longitudinal Study of Aging completed personality

assessments prior to dementia onset (up to 28 years prior); AD neuropathology (severity of neuritic plaques and neurofibrillary tangles stage) was determined by autopsy (Terracciano, et al., 2013). Individuals with AD pathology who remained asymptomatic throughout life had, on average, lower neuroticism. Additionally, the development of clinical dementia was significantly associated with low conscientiousness. In another study, higher neuroticism was associated with smaller regional brain volume and greater decreases throughout the aging process among healthy adults (n=79), while higher conscientiousness was associated with larger regional volumes and less decline with increasing age (Jackson, Balota, & Head, 2011). The developing body of evidence suggests that low neuroticism is associated with resilience to cognitive decline, including AD pathology, while low conscientiousness is associated with increased vulnerability; these patterns indicate links to cognitive reserve which are not yet understood.

The protective role of higher conscientiousness is one that has been explored in more detail. Forstmeier et al. (2012) examined specific motivational abilities that provide individuals with resilience to neuropathology, what they refer to as *motivational reserve*. This motivational reserve encompasses skills important to implementing personal goals including motivating oneself to persevere, quickly coming to a self-congruent decision, readying oneself to act, and self-efficacy. The authors proposed that implementing these motivational abilities throughout one's lifetime increases synaptic connections, strengthens existing pathways, and ultimately leads to efficient brain network utilization as well as compensatory abilities. Older adults without dementia (n=3,327) were followed for three years, assessed at baseline, 18 month, and three year time points. Motivation-related occupational abilities were associated with a reduced risk of MCI and a reduced risk of AD in ApoE ϵ 4 carriers but not non-carriers. These are similar findings to Garibotto et al. (Garibotto, et al., 2012) who found that lifestyle activities help ApoE ϵ 4 carriers compensate through the building of cognitive reserve.

In a population-based longitudinal cohort study by Wang et al. (2009), 506 older adults were followed for up to six years for the development of incident dementia. Neuroticism and extraversion were assessed at baseline using the Eysenck Personality Inventory. In addition to tracking dementia incidence, the study included a measure of leisure activity and social networks in order to categorize subjects based on a higher or lower socially integrated, active lifestyle. Although neither neuroticism nor extraversion were found to be independent predictors of dementia risk, when examined in combination it was found that individuals with low neuroticism in combination with high extraversion were at the lowest risk for dementia. These results remained the same after controlling for active lifestyle, ApoE status, vascular disease, and survival status. In addition, low neuroticism was associated with a decreased risk of dementia in individuals with lower levels of activity or a socially isolated lifestyle. These findings suggest that both personality and personality-environment interactions may contribute to cognitive reserve thereby influencing the risk of dementia development.

Personality and Dementia Interventions

The influence of personality on the outcome of non-pharmacological interventions for dementia has been explored. Also, relationships between premorbid personality and behavioral and psychological symptoms of dementia (BPSD) have been demonstrated (e.g., Archer, et al., 2007; Osborne, Simpson, & Stokes, 2010), as well as the potential for interventions tailored to personality traits to reduce BPSD and increase activity engagement (Kolanowski, et al., 2005; Kolanowski, Litaker, Buettner, et al., 2011). There is also evidence to suggest that individuals with cognitive impairment may respond differently to cognition-focused interventions than the general population based on personality traits.

Relationship between premorbid personality and BPSD. Evidence supports significant relationships between personality and BPSD, which may also influence intervention outcomes. A systematic review that explored the relationship between premorbid personality and challenging behavior in people with dementia found that 72% of the 18 studies reviewed reported significant

relationships between premorbid personality and BPSD (Osborne, et al., 2010). High premorbid neuroticism has been associated with anxiety (Archer, et al., 2007), troublesome behavior (Meins, Frey, & Thiesemann, 1998), aggression (Kolanowski, Strand, & Whall, 1997; Whall, et al., 2008), and delusions (L.-F. Low, Brodaty, & Draper, 2002). Evidence across studies supports a relationship between neuroticism and mood (Osborne, et al., 2010). Higher premorbid agreeableness has been negatively correlated with agitation, irritability, and aggression (Archer, et al., 2007; Kolanowski, et al., 1997). Higher premorbid extraversion has been associated with aggressive behaviors (Kolanowski, et al., 1997). Among individuals with MCI, premorbid neuroticism was positively associated, and premorbid openness to experience negatively associated, with total BPSD symptoms (Mendez Rubio, Antonietti, Donati, Rossier, & von Gunten, 2013), indicating the potential influence of personality on BPSD even in the pre-clinical stages of dementia. Not only may the presence and severity of BPSD influence participation in and benefit from non-pharmacological interventions for dementia, but the identified links between premorbid personality and behavior in dementia supports the sustained influence of premorbid tendencies throughout dementia progression.

Dementia interventions tailored to personality. The influence of personality on behavioral interventions for people with dementia is also empirically supported. When recreational activities for people with dementia were tailored to extraversion and openness as well as functional ability, individuals with moderate to severe AD demonstrated increased activity engagement, attention, alertness, and resultant reduced passivity (Kolanowski & Buettner, 2008; Kolanowski, et al., 2005; Kolanowski, Litaker, Buettner, et al., 2011). Furthermore, these benefits were consistent even for individuals with low premorbid agreeableness, suggesting that the negative effects of low agreeableness when implementing activity interventions may be overcome by tailoring to other personality traits (N. L. Hill, et al., 2010).

A clinical trial of an activity intervention for the behavioral symptoms of dementia randomized 128 nursing home residents with dementia to four treatment groups tailored to: functional level; personality style of interest (extraversion and openness); functional level and personality style of interest; or, an active control condition (Kolanowski, Litaker, Buettner, et al., 2011). After a three week intervention period, participants randomized to either the personality style of interest or functional level and personality style of interest groups demonstrated greater time on task ($p=.005$), level of participation ($p=.000$), more alertness ($p=.003$), and more attention ($p=.024$) than participants in the other groups. These findings indicate that premorbid personality can effectively guide dementia intervention development leading to improved outcomes.

Personality and cognition-focused interventions. Individuals with cognitive impairment may respond differently to cognition-focused interventions than the general population based on personality traits, a possibility that has yet to be explored. For example, although conscientiousness is generally associated with positive health outcomes, when highly conscientious individuals were encouraged to allow errors during the learning process (i.e., to guess), they experienced lower self-efficacy (Gully, Payne, Kiechel Koles, & Whiteman, 2002). In this study, 181 participants were randomized to control, error-encouragement, or error-avoidance conditions and trained to perform a computer-based decision-making task. Findings demonstrated that openness to experience was positively related to knowledge ($r=.21, p<.05$), task performance ($r=.31, p<.05$), and self-efficacy ($r=.19, p<.05$), indicating that these individuals are more likely to excel during training tasks. Conscientiousness was positively related to self-efficacy ($r=.17, p<.05$), which is consistent with patterns of behavior such as achievement orientation and perseverance. However, this relationship was dependent on training context. Highly conscientious individuals who were encouraged to make errors during training reported lower levels of self-efficacy. Therefore, individuals who are strongly motivated and organized may respond poorly to an intervention

when they consistently make incorrect responses, as is likely the case in a person experiencing cognitive decline.

No studies have explored the moderating influence of personality on cognition-focused interventions for persons with dementia. In older adults without dementia, one study found that highly neurotic individuals improved the least following a cognitive training intervention (Yesavage, 1989), and a second study found that those high on the openness trait performed better following the same intervention (Gratzinger, Sheikh, Friedman, & Yesavage, 1990). More recently, an RCT of a cognitive training program for community-dwelling older adults (N=183, MMSE >23) included pretest and posttest measures of personality (Jackson, Hill, Payne, Roberts, & Stine-Morrow, 2012). While there was a significant improvement in the treatment group in inductive reasoning, the targeted area of cognition, there was also a significant increase in openness, independent of improvement in cognitive skill. This study is the first to find that cognitive training among older adults may lead to changes in the personality trait of openness. The evidence base regarding the effect of personality on the outcome of cognition-focused interventions is not developed, and to our knowledge there are no studies reported in samples with dementia.

Personality and Delirium

While the influence of personality on dementia outcomes is a developing body of research, the association between personality traits and delirium has not been well explored. Only one study was identified that examined the relationship between personality traits and delirium incidence (Tully, Baker, Winefield, & Tumbull, 2010). This investigation sought to determine the prognostic risk of incident delirium after cardiac surgery due to affective disorders and Type D personality. Type D personality refers to a tendency toward negative affectivity as well as social inhibition, or to experience increased negative emotions and to not share these emotions with others. It has been conceptualized within the Five Factor Model as high neuroticism, low extraversion, and relatively low conscientiousness

(De Fruyt & Denollet, 2002). Tully, Baker, Winefield, & Tumbull (2010) assessed 158 patients (mean age = 64.7) awaiting elective coronary revascularization surgery for the prevalence of psychiatric disorders and Type D personality. Preoperatively, 13.3% presented with Type D personality. After surgery, 31% of participants experienced delirium. After adjustment for multiple clinical covariates, only depression was significantly associated with delirium incidence ($p=.001$), although Type D personality approached statistical significance ($p=.06$).

Summary: Personality and Cognitive Decline

In summary, personality maintains relatively stable mean-level and rank-order consistency throughout the aging process, particularly in old age. Although modest changes in some personality traits have been demonstrated in mid- to late-life stages, individuals generally maintain a stable personality profile in adulthood, particularly in regard to rank-order consistency of traits. Similarly, mean-level personality changes may occur with the onset of dementia, but the relative strength of personality characteristics within an individual's profile (rank-order consistency) remains stable throughout the early dementia stages. When changes are recognized by family members, they are typically attributable to behavioral symptoms due to disease-related pathology.

Associations between premorbid personality traits and BPSD have been demonstrated in multiple studies indicating that the influence of personality extends into the experience or manifestation of dementia symptoms. Non-pharmacological interventions for dementia have demonstrated improved effectiveness when tailored to individual personality traits. Limited evidence exists regarding the influence of personality traits on cognition-focused intervention outcomes in cognitively intact older adults, and no evidence regarding these effects in individuals with dementia.

Personality and Health-Related Outcomes

Personality traits are important contributors to health-related outcomes as well as treatment success across populations and conditions (e.g., Barry & McCarthy, 2001; Bogg & Roberts, 2004; Conrod, Castellanos-Ryan, & Strang, 2010; O'Leary-Barrett, 2010; Ozer & Benet-Martinez, 2006). The rationale behind these associations is multi-factorial, representing the complexities of personality itself. Causal mechanisms may include relationships between personality and coping, health behavior, and lifestyle patterns, all of which have direct links to physical and psychological health (Kern & Friedman, 2011). Determining the influence of specific traits is equally complex since links between personality and health may be due to a particular trait or the aspects of that trait (referred to as *facets*), combinations of traits working in conjunction, or the social context of a given experience. Although the study of personality effects on health is a complex endeavor, the vast amount of research accumulated in the pursuit has described consistent relationships between certain personality traits and health-related outcomes.

Personality, coping, and health. Individual experience of and response to stress, manifested as variation in appraisal of and coping with stressors, is influenced by personality (Carver & Connor-Smith, 2010). Certain personality traits or patterns of personality are associated with chronically elevated stress responses which may lead to long-term deleterious effects on health (J. E. Graham, et al., 2006). Engagement or approach coping, aimed at dealing with a stressor, is positively associated with higher optimism, extraversion, conscientiousness, and openness (Connor-Smith & Flachsbart, 2007; Malouff, Thorsteinsson, & Schutte, 2005). Disengagement or avoidance coping, aimed at escaping the stressor or related emotions, is related to higher neuroticism while higher optimism, conscientiousness, and agreeableness are related to less disengagement coping. Disengagement coping is generally ineffective and may lead to negative consequences such as prolonged experience of the stressor, increased negative mood and anxiety, and excessive use of drugs, alcohol, or other harmful coping mechanisms (Carver & Connor-Smith, 2010; Najmi & Wegner, 2008). As internal and external stressors accumulate

due to increased challenge or ineffective coping, the body is increasingly susceptible to physical breakdown and illness (McEwen, 1993).

Personality, health behavior, and health. Health behaviors contribute to long-term health outcomes in positive and negative ways, both of which have been associated with personality. While some personality traits, such as neuroticism, are associated with risky health behaviors (Okura, et al., 2010), other traits, such as conscientiousness, predict beneficial outcomes including health-promoting behaviors and treatment success (Bogg & Roberts, 2004; Metzler-Baddeley, 2007; Pernecky, et al., 2009; Petersen & Negash, 2008). The beneficial link among high conscientiousness, physical health, and decreased mortality (Bogg & Roberts, 2004; Kern & Friedman, 2008) is thought to be influenced by improved adaptation to stressors and maintenance of everyday functional abilities (Benjamin Chapman, 2007). Conscientious individuals generally engage in more health protective and less risky behaviors, achieve greater success in educational and career endeavors, and follow healthier living patterns (Bogg & Roberts, 2004). Conscientiousness is not only associated with longevity broadly, but also with longer survival times in individuals with chronic disease (Christensen, et al., 2002).

Alternatively, high neuroticism is associated with psychological distress and maladaptive coping strategies (McCrae & Costa, 2010), which likely contribute to decreased physical self-maintenance and lower functioning in instrumental activities of daily living (IADLs) among older adults (Benjamin Chapman, 2007). Much empirical evidence supports the relationship between neuroticism and negative health outcomes, but overall findings are inconsistent and suggest a more complex relationship (Kern & Friedman, 2011). While some neurotic individuals exhibit pessimism, emotional instability, and hostility leading to negative effects on health, others instead exhibit more anxiety, worry, and watchfulness regarding health leading to an increased attentiveness to health-related needs (Friedman, 2000; Friedman, Kern, & Reynolds, 2010). Although high neuroticism predicts worsened physical health and functioning in older adults and high conscientiousness predicts better physical outcomes, these factors

have also been found to act synergistically such that older adults high in both neuroticism and conscientiousness are healthier than others (Roberts, Smith, Jackson, & Edmonds, 2009). This example illustrates the importance of considering multiple predictors in investigations of personality and health outcomes.

Personality, lifestyle patterns, and health. Individuals select or are drawn toward certain environments, situations, and relationships based, at least in part, on personality tendencies (Buss, 1987; Caspi, et al., 2005; Friedman, 2000, 2008). A lifetime of these choices results in lifestyle patterns that can influence health and well-being outcomes (Kern & Friedman, 2011). The quality and quantity of social relationships is directly influenced by personality (McCrae & Costa, 2002), such as the relationship between high conscientiousness and stable careers and marriages (Roberts & Bogg, 2004). Social relationships, particularly close relationships such as those of spouses, influence health behaviors including adherence to medical treatments, treatment success, quality of life, and physical health (Taylor, 2007). Furthermore, significant life events such as starting a family or new career may be turning points which alter the trajectory of long-term health either positively or negatively depending upon adaptation to the resultant life changes (Kern & Friedman, 2011). Personality, therefore, influences not only the selection of situations which influence health, but also the reactions to these situations and resultant health-related outcomes.

Personality and treatment outcomes. Personality traits are also important to treatment outcomes, particularly conscientiousness which predicts health-promoting behaviors and treatment success (Bogg & Roberts, 2004; Caspi, et al., 2005; Chou & Brauer, 2005; Ozer & Benet-Martinez, 2006). While conscientious individuals tend to be more highly motivated and perform more consistently (Hurtz & Donovan, 2000; Judge & Ilies, 2002), highly neurotic older adults are generally less motivated to perform (Judge & Ilies, 2002) and display detrimental behaviors such as medication non-adherence (Hurtz & Donovan, 2000; Judge & Ilies, 2002). In addition, highly extraverted individuals are more likely

to demonstrate positive rehabilitation outcomes following stroke, likely due to enhanced social functioning (Elmstahl, et al., 1996). These findings suggest that personality traits may influence an individual's participation in and benefit from treatment.

Personality and moderation of health outcomes. Multiple studies have demonstrated the *moderating influence of personality* on health, i.e., the effect of personality traits on the direction or magnitude of relationships between predictors and outcomes (Baron & Kenny, 1986). The Five Factor Model has been investigated for the moderating role of personality traits on the relationship between medical burden and health-related quality of life in older adults (B. Chapman, et al., 2007). Primary care patients (n=442) aged 65 or older completed assessments of cumulative illness, health-related quality of life, mental disorders, IADLs, physical self-maintenance, and personality. Higher neuroticism moderated the relationship between medical burden and impairment in ADLs ($p=.001$) and decreased health-related quality of life ($p<.001$). In another study that examined community-dwelling, older adult couples (n=144) aged 60 to 84, neuroticism demonstrated a moderating effect on the association between physical disability and subjective well-being such that higher neuroticism was associated with poorer subjective well-being in both husbands and wives ($p<.05$; Robb, et al., 2008). Moderating effects of personality may be protective as well. In a study of 55 widows assessed approximately one month following the death of their spouse, personality moderated the effect of stress on life satisfaction ($p=.01$; Rossi, et al., 2007). Specifically, widows who experienced high stress and were highly resilient reported greater life satisfaction than those who experienced high stress but scored low in resiliency. This indicates that those with higher resilience are better able to maintain life satisfaction, or better able to adjust, following a negative life event.

Personality may be particularly important to consider for its influence on chronic disease outcomes. In a study of 162 cancer patients, multiple personality variables were associated with health-related quality of life independent of psychological distress and disease severity (Paika, et al., 2010).

Sense of coherence and denial defense were positively associated with all aspects of health-related quality of life ($p < .05$ to $p < .0005$) and hostility ($p < .01$) and repression defense ($p = .024$) was negatively associated with physical health-related quality of life. While psychological distress was associated with health-related quality of life independent of cancer severity, personality variables moderated these effects such that quality of life was further influenced by personality beyond the association with psychological distress.

The associations between personality and well-being throughout aging, including into late life, were investigated in a long-term longitudinal study of 1,312 participants over approximately four decades (Friedman, et al., 2010). Healthy aging was conceptualized as five categories: physical health, subjective well-being, cognitive functioning, social competence, and productivity. Over the study period, high neuroticism predicted poor late-life subjective well-being ($p < .0001$), physical health ($p < .0001$), social competence ($p = .03$), and productivity ($p = .04$), but was not related to mortality risk ($p = .61$). While neuroticism was the strongest predictor of subjective well-being for the entire sample, there were other gender differences. In men, agreeableness was the strongest predictor of physical health, extraversion the strongest predictor of social competence, and conscientiousness the strongest predictor of productivity. In women, neuroticism was the strongest predictor of physical health and extraversion the strongest predictor of social competence. Across the sample, high conscientiousness predicted lower mortality risk ($p = .003$). These findings indicate that personality may influence health directly as well as via moderating influences such as subjective well-being in the presence of chronic or debilitating disease.

The moderating influence of personality on health behaviors and treatment outcomes has also been investigated. Conscientiousness was found to significantly ($p < .05$) moderate the relationship between intention and exercise behavior in a sample of 146 college-age adults (Conner, et al., 2007). In a sample of 410 community-dwelling adults aged 26 to 87, neuroticism moderated ($p < .001$) the

relationship between intention and healthy food choices (de Bruijn, et al., 2009). Due to the effect of personality on health behaviors and treatment outcomes, the potential of interventions tailored to personality traits has been examined, and the effectiveness of personality-based interventions in children and adolescents has been widely demonstrated (Conrod, 2008; Conrod, et al., 2010; McClowry, Rodriguez, & Koslowitz, 2008; O'Leary-Barrett, 2010).

Summary: Personality and Health-Related Outcomes

In summary, the Five Factor Model has been used extensively in personality and health research and offers several distinct advantages as a framework for investigating the effects of personality traits on health and treatment outcomes. While the links between personality and health have been substantiated, the causal mechanisms of such links are likely multi-factorial and complex. Personality has a demonstrated influence on health and treatment outcomes across populations and conditions as well as a moderating effect on health outcomes. Most notably, higher neuroticism is consistently associated with poorer, and higher conscientiousness with better, health-related outcomes.

Moderators of Cognition-Focused Outcomes

Although multiple studies implementing cognition-focused interventions have demonstrated positive outcomes in people with dementia (e.g., Clare, et al., 2010; Spector, et al., 2003), not all have found benefits and the evidence base overall is undeveloped (Papp, et al., 2009). While much of the variability is likely due to differences in intervention approaches and methodological quality, another consideration is whether some individuals are better candidates than others for cognition-focused interventions.

A review of the clinical expression of neurodegenerative disorders concluded that multiple factors should be considered when selecting interventions for individuals with dementia including awareness, personality style, as well as use of defense mechanisms and coping strategies (Clare & Woods, 2003; von Gunten, et al., 2009). Factors such as these may be moderators of intervention

success in cognition-focused interventions. Moderator variables are those that influence the degree or direction of an effect, and may improve the ability to make a causal inference regarding the outcome of a treatment (Shadish, et al., 2002). Determining statistically significant moderators allows investigators to characterize the individuals likely to respond and identify best candidates for that particular treatment (Baron & Kenny, 1986; Kraemer, et al., 2008); hence, the effect size in future research may be maximized when the sample selected has characteristics which improve treatment effectiveness. The consideration of moderating influences in cognition-focused intervention research is notably absent in the empirical evidence. Within nursing science specifically, it has been recommended that moderators be considered to determine the circumstances in which a nursing intervention provides the best outcome (J. A. Bennett, 2000).

Chapter 2 Summary

Among individuals at risk for accelerated cognitive decline, personality may moderate the effectiveness of a cognitively stimulating activity intervention to improve cognitive functioning. The relationship between personality and health is well-established and accepted, including the moderating influence of specific “Big Five” personality traits on treatment outcomes. Personality may be considered dynamically stable over the lifespan such that individuals maintain a largely consistent personality profile with relatively modest changes. When personality change does occur during adulthood, and particularly late adulthood, it is typically mean-level change of small magnitude with preservation of rank-order consistency. The stability of personality throughout the early stages of dementia follows this same pattern of mean-level normative change, but preservation of overall rank-order consistency of personality traits in relation to other individuals. Personality stability throughout aging and early-stage dementia provides the opportunity to utilize measures of premorbid personality in interpretation of behavior after dementia diagnosis. The consistent influence of premorbid personality on persons with dementia is further supported by demonstrated relationships between premorbid personality and BPSD

as well as the effectiveness of dementia interventions targeted to premorbid personality. Certain personality traits may predispose vulnerable individuals to delirium, but the evidence is not yet well-established.

Although dementia and delirium are independent clinical diagnoses, they are extensively interrelated and may share common pathogenic mechanisms. The development of acute confusion in a person with dementia represents the exacerbation of cognitive deficits in an already vulnerable individual. Life-altering and costly negative outcomes frequently result including accelerated cognitive decline, decreased quality of life, and increased mortality. Although dementia is chronic and progressive, acute confusion and its consequences may be reversed if effectively treated.

Cognitive reserve is thought to provide a protective effect against brain pathology such as AD. Multiple studies have demonstrated the link between lifestyle factors such as educational and occupational attainment (proxies of cognitive reserve) and decreased dementia risk. This protective effect may be due to the cognitively stimulating nature of such activities. The engagement in cognitively stimulating activities during late life has been shown to decrease dementia risk as well as slow dementia progression among those diagnosed. It is thought that this effect is due to retained plasticity mechanisms in the brain which provide for modification of neuronal connections leading to compensation for brain damage and preservation of function. Empirical evidence supports the ability of individuals with early-stage AD to utilize such compensatory processes. Brain plasticity may be targeted through cognitively stimulating activities in individuals with cognitive impairment, leading to increased cognitive reserve and preservation or improvement of cognitive functioning.

Cognition-focused interventions for individuals with dementia have sought to trigger plasticity mechanisms in order to improve function. Cognitive stimulation is an approach to cognition-focused intervention which is empirically supported and has demonstrated improvements in multiple cognitive domains among individuals with cognitive impairment. Interventions for the treatment of delirium,

however, are largely absent from the literature. Although guidelines for prevention of delirium have been established, the management of incident delirium is much less researched. Few interventions for delirium treatment have been tested and most demonstrate no improvements. Similarly, only one intervention for delirium in those with preexisting dementia has been investigated, although this approach which utilizes cognitively stimulating activities has demonstrated promising preliminary results.

Although cognitive stimulation interventions hold promise for individuals experiencing cognitive decline, much remains to be understood regarding their effectiveness among different individuals. Moderators influence the effect of an intervention: an alteration in degree or direction. Determining moderators of treatment effect helps to identify individuals who are best candidates for a particular treatment. Considering the established influence of personality on health and treatment outcomes as well as its demonstrated effect in individually tailored dementia interventions, the consideration of personality as a moderator of the effect of a cognitively stimulating intervention for delirium in persons with dementia is well-supported.

Chapter 3

Methods

This exploratory study investigated whether premorbid personality moderated the treatment effect of a cognitively stimulating activity intervention in individuals with dementia experiencing acute cognitive decline (delirium). Premorbid personality is conceptualized according to the five factor model in which the traits of neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness are each measured to provide a comprehensive view of the structure of one's personality traits (McCrae & John, 1992). The outcomes of interest were cognitive function (attention, orientation, memory, and executive function) and engagement in the intervention. Therefore, study methods tested the effects of the five personality factors on the four identified domains of cognitive functioning as well as participation (engagement) in the intervention. The study's overarching aims were as follows:

1. To test the moderating effects of personality traits on the relationship between a cognitive stimulation intervention and improvement in four domains of cognitive function (attention, memory, orientation, and executive function) during a period of acute cognitive decline in persons with dementia.
2. To test the effects of personality traits on engagement in the intervention during a period of acute cognitive decline in persons with dementia.

Study Design

The study utilized a portion of the sample participating in a randomized repeated measures clinical trial, Recreational Stimulation for Elders as a Vehicle to Resolve Delirium Superimposed on Dementia (RESERVE-DSD), currently funded by the National Institutes of Health (R01 NR012242). The parent study, RESERVE-DSD, is continually enrolling subjects over a five year period; however, this study included a portion of the parent study subjects consecutively enrolled during the study period, October

1, 2011 to January 31, 2013. In addition to including data collected within RESERVE-DSD, a personality assessment was added in order to test for a moderating effect not included in the original study design. These data were collected prospectively by the Principal Investigator (PI) of the study as subjects were enrolled in the parent study. Subjects were recruited and enrolled at admission to a post-acute care facility, then randomly assigned to intervention (RESERVE-DSD) or control (usual care) groups.

Randomization Procedure

Randomization of the parent study sample was conducted by a statistician prior to subject enrollment. A random number generator was utilized with randomization conducted in blocks by nursing home site and time, thus maintaining approximately equal groups throughout the study period. This procedure ensured that the data utilized in this study had approximately equal numbers in treatment and control groups.

Randomization was implemented by subject rather than by site. Treatment allocation was obtained from a centralized location and group assignment remained concealed until screening, consent, and assignment of study identification number were complete. Although randomization was employed to control for extraneous variance, it is acknowledged that other variables may impact study findings. Therefore, the parent study employs strict enrollment criteria to control for these confounding influences. Additionally, analyses in this study included several covariates to further control potential sources of extraneous variance.

Intervention Protocol

The intervention, referred to herein as RESERVE-DSD (Kolanowski, Hill, Clare, & Marx, 2012), was delivered to subjects in the treatment group in conjunction with the care and therapies typically prescribed for their medical or surgical condition. RESERVE-DSD consists of mentally challenging recreational activities which incrementally increase in task difficulty and are tailored to each subject's interests and functional abilities. These recreational activities are delivered by trained RAs once a day for

30 days or until discharge, beginning within 72 hours of admission to the post-acute care facility.

Subjects receive up to 30 minutes of individually prescribed recreational activities once a day during the afternoon for up to 30 consecutive days (exclusive of weekends) during the study period. A thorough description of the intervention protocol is provided in Appendix A.

Activities selected by the principal investigators of the parent study provide mental stimulation in multiple cognitive domains. Groups of activities were chosen that stimulate each of the four cognitive domains of interest: attention, orientation, memory, and executive function. Based on each subject's dementia stage, physical function, and activity interests, a personally tailored prescription of activities is determined. The goal of the intervention is to activate cognitive processing and as such, RAs encourage the subject to actively engage in each activity, providing motivation and verbal encouragement throughout the session.

In order to monitor and improve the reliability of the intervention, RAs are trained in these recreational activities and practice in simulated sessions until they achieve 100% agreement on all critical elements before implementing the intervention in the field. Treatment fidelity is monitored throughout the study: 10% of all intervention sessions are randomly selected for monitoring of critical aspects of treatment fidelity. If treatment fidelity is not obtained for any aspect of the protocol, retraining of the RA is initiated.

Usual Care Condition

The control group received routine nursing care as typically delivered for their particular health condition and participated in all routinely prescribed therapies.

Setting

The study was conducted in seven nursing homes with post-acute care services for rehabilitation following hospitalization. All facilities are located in Northeast, Central, and South-central Pennsylvania: 240-bed Centre Crest, 157-bed Hearthside, 404-bed Spring Creek, 120-bed Windy Hill, 116-bed

Brookline, 130-bed The Meadows, and 180-bed Mountain View. These sites represent a mix of for-profit, non-profit, county-owned, rural and urban, as well as large and medium community-based settings.

Sample

Potential subjects were screened upon admission to the post-acute care facility for the following inclusion criteria: English speaking; 65 years of age or older; community-residing prior to most recent hospitalization; diagnosis of dementia; presence of delirium; and having a responsible party (typically a spouse or adult child) to provide medical history, education, occupation, leisure, and personality data. Exclusion criteria were as follows: having any neurological or neurosurgical disease associated with cognitive impairment other than dementia including Parkinson's disease with Lewy Body dementia, Huntingdon's disease, normal pressure hydrocephalus, seizure disorder, subdural hematoma, head trauma, or known structural brain abnormalities; frontotemporal dementia; nonverbal; having a life expectancy of six months or less; acute major depression; and severe hearing or vision impairment.

After initial eligibility determination, subjects were further screened for mild to moderate stage dementia through subject and informant interviews using the Modified Blessed Dementia Rating Scale (MBDRS; Blessed, et al., 1968) and Clinical Dementia Rating Scale (CDR; Hughes, Berg, Danziger, Coben, & Martin, 1982), as well as for the presence of delirium using the Confusion Assessment Method (CAM; Inouye, et al., 1990) and the Mini-Mental State Exam (MMSE; Folstein, et al., 1975). The MBDRS is a validated informant-based tool for discriminating demented and non-demented individuals based on DSM-III-R criteria (Froehlich, Robison, & Inouye, 1998). Scores on the MBDRS range from 0 to 17 and a score greater than three is consistent with dementia. The CDR stages dementia on a 0 to 3 scale; zero indicates no dementia and three indicates severe dementia. Subjects who scored a three or greater on the MBDRS and from 0.5 to 2.0 on the CDR were considered eligible as these two scores indicate the presence of mild to moderate stage dementia. The CAM is a validated tool for determining the presence

of delirium based on a standardized algorithm (Wei, Fearing, Sternberg, & Inouye, 2008). Individuals with at least two features of delirium identified in the CAM were considered eligible. The MMSE is a 30-item cognitive screen, with established reliability, which measures orientation, memory, attention, and language with scores ranging from 0-30 (higher scores indicate greater cognitive function). All dementia and delirium diagnoses were adjudicated by a panel of three experts: a geriatrician, neurologist and neuropsychologist. Those subjects meeting all enrollment criteria were invited to participate in the study. Additionally, the Charlson Co-morbidity Index (van Doorn, et al., 2001), a weighted index that takes into account the number and seriousness of co-morbid diseases, was used to further characterize the study sample.

The sample for this study consisted of 71 subjects (38 treatment and 33 control) from the parent study; this constitutes a reasonable sample size for testing the specified aims in an exploratory study. A sample size of 70 participants (35 per group) yields 80% statistical power with a two-sided, 0.05 significance level test to detect an effect size of 0.68 standard deviation units. The investigation of Aim 2 utilizes subjects in the intervention group only (n=38); therefore, these analyses are considered preliminary in nature.

Measures

The measures used in the analyses consisted of both data extracted from the larger database of the parent study as well as the personality measure collected prospectively from the subjects' knowledgeable informants by the PI. A copy of all instruments relevant to this study can be found in Appendix B.

Baseline Measures

Baseline data were extracted from the database of the parent study including demographic characteristics (age, gender, and race/ethnicity), ApoE ϵ 4 status, Lifetime of Experiences Questionnaire (Valenzuela & Sachdev, 2007), and MBDRS scores. These measures were used as covariates in the

analysis because they could impact the outcome variables and in order to control for potential imbalances between the two groups. In addition, the NEO™ Personality Inventory-3 (McCrae & Costa, 2010), which assesses the moderating variables of interest, was collected at baseline. These measures are discussed in more detail below.

ApoE ε4 Status. ApoE ε4status was obtained by extracting DNA from buccal swab samples using the protocol of the Institute of Psychiatry in London (Freeman, et al., 2003). Each individual may have up to two ε4 alleles; therefore, ApoE ε4status was quantified as the presence of 0, 1, or 2 ε4 alleles. Higher numbers of ε4 alleles are associated with greater risks for cognitive impairment (Ertekin-Taner, 2007; Greenwood, et al., 2005).

Lifetime of Experiences Questionnaire (LEQ). The LEQ provides a measure of complex mental activities over the lifetime including educational, occupational, and leisure lifestyle activities that measure cognitive lifestyle, a proxy measure for cognitive reserve. Higher LEQ scores indicate higher lifetime levels of complex mental activity. The LEQ has demonstrated an internal consistency of .66 and test-retest reliability of .98 (Valenzuela & Sachdev, 2007).

Modified Blessed Dementia Rating Scale (MBDRS). The MBDRS, as previously discussed in regard to the study sample, discriminates between demented and non-demented individuals based on DSM-III-R criteria, with higher scores indicating greater dementia-related impairment.

NEO™ Personality Inventory-3 (NEO™-PI-3). An additional baseline measure, premorbid personality, was collected by the PI. Premorbid personality refers to personality prior to the onset of dementia symptoms. It was measured using an instrument based on the five factor model of personality, the informant version of the NEO™-PI-3 (McCrae & Costa, 2010). Five personality traits are measured: neuroticism, extraversion, openness, agreeableness, and conscientiousness. Each of the 240 items is rated on a five-point scale (strongly disagree, disagree, neutral, agree, and strongly agree); 48 items measure each of the five personality traits. Raw scores on each trait range from 0 to 48, but are

considered meaningful only when compared to appropriate norms (McCrae & Costa, 2010). Therefore, raw scores were converted to T scores with a mean of 50 and standard deviation of 5 using adult normative data for the purposes of analysis and interpretation.

The *NEO™* personality inventories are commonly used in the measurement of premorbid personality in individuals with dementia utilizing a retrospective assessment by the subject's knowledgeable informant, typically a spouse, adult child, or sibling (Archer, et al., 2006; Kolanowski & Litaker, 2006; Kolanowski, et al., 2005). All informants met criteria specified by Ritchie and Fuhrer (1996) for knowledgeable informants: a person having had at least monthly contact with the subject for at least three years prior to dementia diagnosis. The use of an informant is necessary due to the inability of the subject to complete the assessment as a result of cognitive impairment, particularly the acute decline associated with delirium.

Measurement of premorbid personality, or personality prior to the onset of dementia symptoms, is an approach that has been used successfully in multiple scientific investigations (e.g., Archer, et al., 2007; Kolanowski, et al., 2005; Kolanowski, Litaker, Buettner, et al., 2011; Song & Algase, 2008; Strauss, Pasupathi, & Chatterjee, 1993; von Gunten, et al., 2009). Although modest changes in personality may occur over one's lifetime, personality remains relatively stable throughout the aging process (Terracciano, et al., 2006; Terracciano, et al., 2010) as well as throughout the moderate stages of dementia (Kolanowski & Whall, 1996; Twigg, et al., 2007). Therefore, the personality of an individual with early-stage dementia is predominantly the same as it was premorbidly, particularly in regard to rank order stability of traits (Dawson, et al., 2000). Premorbid measures of personality are preferred because it is often difficult for informants to disentangle dementia-related behaviors from current personality. Therefore, informant rating of personality prior to dementia onset is thought to provide a more valid assessment.

Daily Measure (Covariate)

Confusion Assessment Method (CAM). The CAM is a standardized screening algorithm which allows individuals without formal training to quickly and accurately identify delirium. It was administered daily, for up to 30 days, by trained RAs. The CAM measures four features: 1) acute onset and fluctuating course, 2) inattention, 3) disorganized thinking, and 4) altered level of consciousness (Inouye, et al., 1990). A subject is scored as having subsyndromal delirium if they exhibit any two features and full delirium if they exhibit features one and two and either three or four (Voyer, Richard, Doucet, & Carmichael, 2009). For the purposes of analysis, daily CAM scores were coded as 0 (no delirium), 1 (subsyndromal delirium), or 2 (full delirium). The CAM was validated against geriatric psychiatrists' ratings using DSM-III-R criteria and has been shown to have a sensitivity between 94% and 100% and a specificity between 90% and 95% (Inouye, et al., 1990; Pompei, Foreman, Cassel, Alessi, & Cox, 1995). The CAM has also been validated in persons with dementia. Studies have shown the utility of a daily CAM in identifying delirium and its waxing and waning states (Han, et al., 2001). The CAM score was used as a time-dependent covariate measure within the analysis in order to control for the daily fluctuations of delirium status within subjects.

Outcome Measures

Five main outcomes are examined in this study: performance in four domains of cognition (attention, orientation, memory, and executive function) and engagement in the intervention. Cognitive performance was measured for both intervention and control groups each day during the subjects' participation in the study, up to 30 days. A separate group of RAs, blinded to condition assignment, were used to collect these data.

Digit Span. This instrument, which measures attention, is a subtest of the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1981). The *Digit Span* consists of asking the subject to repeat a series of numbers, increasing in length, first forward and then backward. The assessment ends when the

subject fails to correctly repeat two sequences in a row. The reliability of the *Digit Span* has been demonstrated as .97 for the forward series and .96 for the backward series (Palmer & Meldon, 2003; Ramsay & Reynolds, 1995). Total *Digit Span* scores range from 0 to 30 with higher scores representing better attention as well as working memory.

Montreal Cognitive Assessment (MoCA). Orientation and memory were measured using a shortened version of the *MoCA* (Nasreddine, et al., 2005), a brief cognitive assessment that is frequently used in geriatric populations with cognitive impairment. The *MoCA* items utilized are brief assessments of orientation to person, time, and place, short-term memory, and delayed recall. It has demonstrated good internal consistency reliability with a Cronbach's alpha of up to .83 (Tasha Smith, Gildeh, & Holmes, 2007) and better consistency in clinical samples (Bernstein, Lacritz, Barlow, Weiner, & Defina, 2010). Orientation scores were calculated based on the sum of seven orientation items. Memory scores were calculated as the total correct responses on two instances of three-word recall, resulting in a total possible score of six on Memory.

CLOX. Executive function was measured using the *CLOX* (Royall, Cordes, & Polk, 1998), a clock drawing task consisting of both free drawing and copying tasks. Scores on each of the two parts of the *CLOX* range from 0 to 15 with higher scores indicating better executive function; these scores are added together to obtain a total *CLOX* score. The *CLOX* has demonstrated an internal consistency of .82 and inter-rater reliability of .93 to .94.

This study also investigated engagement in the intervention as an outcome. Two measures of engagement are collected in the parent study: time on task and level of participation. Time on task is measured by the RA during the implementation of the intervention using a stop watch. Minutes and seconds of total time engaged in the intervention are measured, ranging from 0 to a maximum of 30 minutes. Inter-rater reliability in a previous study demonstrated a percentage agreement of 93.6 and a weighted kappa of 0.91 (Kolanowski, Litaker, Buettner, et al., 2011). In addition, the RA determines a

level of participation rating using a scale established by Kovach and Magliocco (1998) with scores ranging from 0 (dozing) to 3 (active participation). Previous inter-rater reliability on this scale was a percentage agreement of 98.2 and a weighted kappa of 0.96 (Kolanowski, Litaker, Buettner, et al., 2011). These two measures were combined to determine an overall daily engagement measure by multiplying the daily time on task by the level of participation rating.

Data Collection and Management

All data except the *NEO™-PI-3* assessment results were collected by RAs within the parent study and were extracted from the RESERVE-DSD database. All parent study data are managed by the Social Science Research Institute (SSRI) in accordance with the established Data and Safety Monitoring Plan for RESERVE-DSD. Dr. Kolanowski supervised the data transfer to the PI, ensuring that only the selected measures were included and subject confidentiality was maintained.

Administration of the *NEO™-PI-3* questionnaire was completed by the PI via telephone or mail utilizing the subject's knowledgeable informant. *NEO™-PI-3* responses were entered into hard copy answer sheets by the PI and subsequently entered into a computer program for data entry and scoring available from Psychological Assessment Resources, Inc. This database was exported for merger with the selected measures extracted from the RESERVE-DSD database.

Data Safety and Monitoring Plan

A Data and Safety Monitoring Committee is in place for the parent study. Three individuals who are not involved in the study provide oversight and monitoring. The committee meets yearly to evaluate data quality and timeliness, subject recruitment, accrual and retention, and subject risk versus benefit. Confidentiality of the proceedings of these meetings is maintained.

Protection of Human Subjects

Human subjects in the study included: 1) participants in the clinical trial, the primary sample; and 2) the responsible parties of the primary sample, the informational sample. The primary sample

includes participants in the parent study, a Phase II Clinical Trial (R01 NR012242). Primary subjects met the same eligibility criteria as subjects in the parent study, were exposed to the same potential risks, and received the same protection from such risks. Due to the presence of active delirium in addition to a baseline dementia diagnosis in each primary subject at enrollment, a legally authorized representative provided consent for participation in the study. The informational sample was comprised of these responsible parties, one for each primary subject. Responsible parties consented to provide information regarding the primary subject, including completing a personality assessment.

Sources of materials. Data were obtained from six sources: informational subject interview, primary subject interview, medical chart review, cognitive testing of primary subject, direct observation of primary subject, and buccal cavity cell samples from primary subject for DNA extraction. Data were collected for research purposes only and were coded to preserve subject confidentiality. Raw data were stored in locked file cabinets in the locked research office of the project director of the parent study. Only authorized research personnel had access to these data. Research staff were prohibited from taking data elsewhere. Data were taken to the Social Science Research Institute, entered into an SPSS computer program, and verified.

Recruitment and Informed Consent. The parent study was approved by the Pennsylvania State University Institutional Review Board (IRB) prior to study commencement. Every precaution was taken to protect the autonomy of subjects and to ensure that consent was informed. All Office for Research Protections (ORP) policies for the conduct of research involving human subjects were followed including HIPAA guidelines for the protection of health information and protection of subjects with dementia as a vulnerable population.

The primary subject's legally authorized representative provided consent to participate due to the current cognitive status of the primary subject at baseline; all primary subjects had a diagnosis of dementia and were experiencing an episode of delirium. The acute confusion characteristic of delirium

ethically prevented primary subjects from providing consent. However, daily assent was obtained from all primary subjects for assessments and intervention and this assent is documented. Confidentiality of all subjects is assured in the collection, analysis, and reporting of data. The “Consent for Participants and Responsible Party” (See Appendix C) is thoroughly reviewed by the project director and both the legally authorized representative and the primary subject signed the form to provide written consent.

Data Analysis

Descriptive statistics for all variables measured at baseline were stratified according to randomized group (treatment vs. control) to assess how the two groups compared qualitatively. The statistical analyses were based on the linear mixed-effects model in order to account for the longitudinal data from the 30-day post-randomization measurement period. This model is most appropriate for hierarchical data with multiple observations collected over time on the same individuals; such was the case with the repeated outcome measures this study.

The statistical models included terms to account for the following baseline covariates, nested within each of the intervention and control groups: nursing home facility, age, gender, ApoE ϵ 4 status, MBDRS, and LEQ. Additionally, the daily CAM score was included as a time-dependent covariate in the analyses. For Aim 1, interaction terms for the five personality variables (neuroticism, extraversion, openness to experience, agreeableness, conscientiousness) by treatment group were included to test for the moderating effects of personality on each of the four cognitive outcomes. For Aim 2, which included the treatment group only, personality variables were included as main effects in the analysis.

Chapter 4

Results

Sample Characteristics

The sample consisted of 71 subjects, randomly assigned to treatment (n=38) and control (n=33) groups. As previously described, all subjects had a baseline diagnosis of mild to moderate dementia as well as at least two features of delirium at study enrollment. Baseline characteristics of the study sample are provided in Table 4.1. The distribution of the sample by study site is provided in Table 4.2.

Table 4.1. *Baseline Characteristics of the Study Sample*

	Treatment Group (n=38)	Control Group (n=33)	Total (n=71)	p-value	Min	Max
	%/Mean(SD)	%/Mean(SD)	%/Mean(SD)			
Age	85.0 (5.2)	85.0 (5.8)	85.0 (5.4)	.96	65	95
Gender (% female)	63.2%	60.6%	62.0%	.82	---	---
Race (% Caucasian)	100%	100%	100%	--	---	---
CDR Score	1.2 (0.5)	1.3 (0.6)	1.3 (0.6)	.96	0.5	2.0
MBDRS Score	6.2 (2.7)	7.1 (2.4)	6.6 (2.6)	.14	3.0	13.0
MMSE	13.8 (7.0)	13.1 (5.3)	13.5 (6.2)	.63	0	30
LEQ Score	70.0 (15.2)	68.5 (15.6)	69.3 (15.3)	.68	38.8	117.5
ApoE ε4 (% no ε4)	68.4%	64.5%	66.7%	.34	0	2
Charlson	1.8 (1.5)	1.8 (1.4)	1.8 (1.5)	.97	0	6

For categorical variables, p-values are based on results from chi-square tests. For continuous variables, p-values are based on results from t-tests for equality of means.

CDR = Clinical Dementia Rating; range 0 (no dementia) to 3 (severe dementia) scale

MBDRS = Modified Blessed Dementia Rating Scale; range 0 to 3, higher scores indicate greater impairment

LEQ = Lifetime of Experiences Questionnaire; range 0 to 162, higher scores indicate greater complex mental activities across the lifespan (proxy cognitive reserve measure)

Charlson = Charlson Co-Morbidity Index; range 0 to 37, higher scores indicate co-morbidity burden

MMSE = Mini-Mental State Examination; range 0 to 30, higher scores indicate higher cognitive function

The study sample was primarily female, entirely Caucasian, and 85 years of age on average.

Summary statistics indicate a sample with a relatively moderate level of cognitive impairment, which is congruent with inclusion criteria. Approximately one-third of the sample had at least one ApoE ε4 allele.

On average, subjects had a relatively low co-morbidity burden beyond their baseline dementia

diagnosis, which is given a score of 1 in the weighted index. There were no significant differences ($p > .05$) between groups on any of the baseline characteristics.

Table 4.2. *Sample Distribution by Study Site (Nursing Home Facility)*

	Treatment Group (n=38)	Control Group (n=33)	Total (n=71)
Centre Crest	26.3%	27.3%	26.8%
Hearthside	7.9%	3.0%	5.6%
Windy Hill	7.9%	12.1%	9.9%
Spring Creek	18.4%	15.2%	16.9%
Brookline	21.1%	21.2%	21.1%
The Meadows	13.2%	6.1%	9.9%
Mountain View	5.3%	15.2%	9.9%

The majority of the study sample was from two of the seven nursing home facility sites, Centre Crest and Brookline, although all seven sites were represented by a minimum of approximately 10% of the total sample.

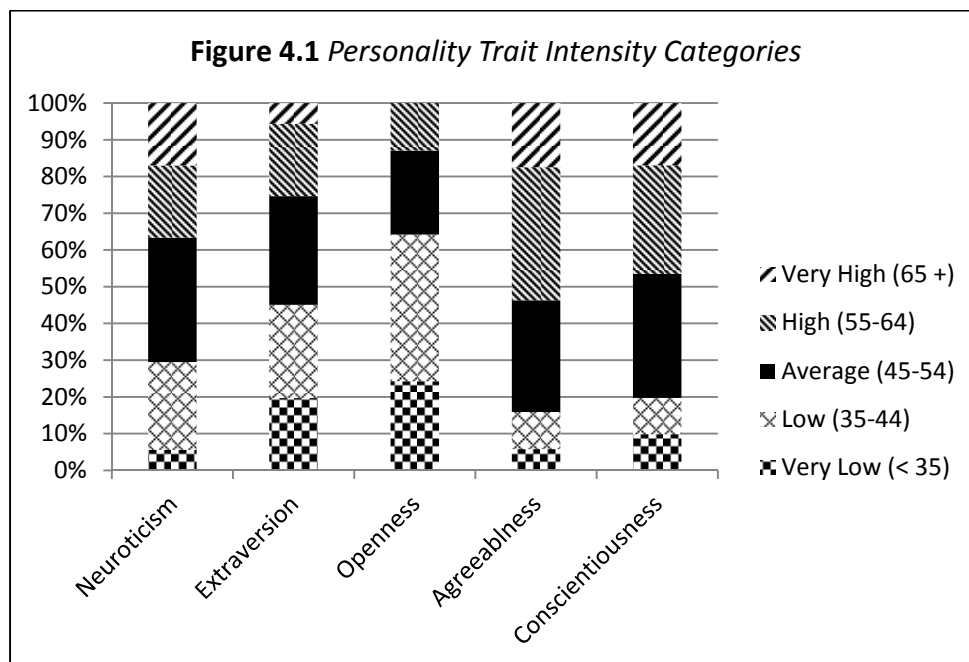
Subject personality trait scores (neuroticism, extraversion, openness, agreeableness, and conscientiousness) were converted from raw scores to T scores using adult normative data provided by Psychological Assessment Resources, Inc. Therefore, an individual score of 50 on one of the five traits indicates a score equivalent to the mean of the normative sample. Table 4.3 displays the average scores for each personality trait across groups. Figure 4.1 shows the cumulative percentages for the five intensity categories (ranging from very low to very high) for each trait score. Openness and agreeableness scores were unable to be calculated in a total of three instances due to the inability of the knowledgeable informant to provide responses to enough items in these categories for accurate scoring.

Table 4.3. *Mean Personality Trait T Scores by Treatment Group*

	Treatment Group Mean(SD)	Control Group Mean(SD)	Total Mean(SD)	p-value	Min	Max
Neuroticism (n=71)	53.0 (12.5)	49.6 (9.5)	51.4 (11.3)	.21	26	78
Extraversion (n=71)	46.0 (12.9)	46.5 (12.1)	46.2 (12.5)	.86	15	84
Openness (n=70)	43.1 (11.0)	38.8 (9.9)	41.1 (10.6)	.09	15	62
Agreeableness (n=69)	55.7 (13.0)	53.1 (11.6)	54.5 (12.3)	.38	18	81
Conscientiousness (n=71)	52.8 (11.3)	52.3 (13.4)	52.6 (12.2)	.86	19	80

P-values are based on results from t-tests for equality of means.

Personality trait T scores displayed a wide range for all five variables and mean scores were within 5 points of a score of 50, with the exception of openness which had a mean of approximately 41. There were no significant differences ($p > .05$) between groups on the five personality trait scores, although openness approached significance with a p-value of .09.



As displayed in Figure 4.1 above, the division of personality traits scores by intensity level (very high, high, average, low, and very low) as compared to a normative sample indicates several skewed distributions. This is most notable in regard to openness, which tended to score lower than average and agreeableness which tended to score higher.

Data Analysis

This exploratory study investigated whether premorbid personality is a moderator of treatment effect of a cognitively stimulating activity intervention in individuals with dementia experiencing an acute episode of cognitive decline. Results of the analyses are presented according to the study aims.

Aim 1: Test the moderating effect of personality traits on the relationship between a cognitive stimulation intervention and improvement in four domains of cognitive function (attention, memory, orientation, and executive function) during a period of acute cognitive decline.

Table 4.4 displays the summary statistics for the four cognitive outcomes by treatment group. These indicate the average of all scores for each measure across all days.

Table 4.4. Summary Statistics for Cognitive Outcomes

Cognitive Domain (Measure)	Treatment Group	Control Group	Total	Min	Max
	(n=38)	(n=33)	(n=71)		
	%/Mean(SD)	%/Mean(SD)	%/Mean(SD)		
Attention (Digit Span)	11.4 (5.4)	10.9 (4.9)	11.1 (5.2)	0	29
Memory (MoCA)	2.0 (2.4)	1.9 (2.2)	2.0 (2.3)	0	6
Orientation (MoCA)	3.7 (2.2)	3.6 (2.1)	3.7 (2.1)	0	7
Executive Function (CLOX)	17.2 (8.1)	12.7 (8.0)	15.0 (8.4)	0	30

Digit Span range = 0 to 30; MoCA (Montreal Cognitive Assessment) Memory range = 0 to 6, Orientation range = 0 to 7; CLOX range = 0 to 30

Table 4.5 displays the treatment effect (adjusted for all of the covariates) for each of the four cognitive outcomes, across models. These results show that, in this sub-sample, the treatment had a statistically significant effect on one of the four cognitive outcomes: executive function.

Table 4.5. Adjusted Means (Standard Errors) for the Treatment Groups and Their Differences for the Four Cognitive Outcomes

	Treatment Group	Control Group	Difference	Group	p-value
	Adjusted Mean (Std Error)	Adjusted Mean (Std Error)	Between Adjusted Means (Treatment – Control)	Comparison Estimate (Std Error)	
Attention	11.66 (0.87)	11.88 (0.87)	-0.22	-0.22 (0.96)	.816
Memory	1.69 (0.39)	2.04 (0.39)	-0.35	-0.35 (0.45)	.438
Orientation	3.94 (0.43)	3.71 (0.39)	0.23	0.23 (0.45)	.614
Executive Function	18.06 (1.64)	12.46 (1.44)	5.60	5.60 (1.57)	<.001*

* p-value < .05

Tables 4.6 through 4.9 display the baseline covariate, time-dependent covariate, main personality effects, and interaction effects for each of the four cognitive outcomes. Interactions of personality traits by treatment group reflect moderating effects of the personality variables on the

association between treatment group assignment and the designated cognitive outcome. For the purposes of this exploratory analysis, main effects were considered significant at the $\alpha=.05$ level and interaction effects at the $\alpha=.10$ level; all discussion of significant effects follows that designation.

Table 4.6. *Moderating Effects of Personality on the Association between Treatment Group and Attention*

Effect		Estimate (Std Error)	p-value
Treatment Group Comparison		-0.22 (0.96)	.816
Baseline Covariates			
Age		0.26 (0.09)	.005**
Gender		0.05 (0.62)	.940
ApoE ϵ 4		-1.62 (1.11)	.144
MBDRS	Control	0.11 (0.37)	.773
	Treatment	-0.73 (0.32)	.023**
LEQ	Control	0.15 (0.07)	.040**
	Treatment	0.18 (0.06)	.002**
Time-Dependent Covariate			
CAM	Control	-1.78 (0.23)	<.0001**
	Treatment	-1.36 (0.25)	<.0001**
Main Effects of Personality			
Neuroticism	Control	0.10 (0.09)	.266
	Treatment	-0.01 (0.06)	.936
Extraversion	Control	-0.14 (0.07)	.037**
	Treatment	-0.03 (0.07)	.649
Openness	Control	0.03 (0.08)	.692
	Treatment	-0.14 (0.07)	.047**
Agreeableness	Control	0.12 (0.07)	.101
	Treatment	0.13 (0.07)	.060*
Conscientiousness	Control	-0.09 (0.05)	.085*
	Treatment	-0.08 (0.09)	.329
Moderators			
Neuroticism by Treatment Group		-0.10 (0.11)	.335
Extraversion by Treatment Group		0.11 (0.09)	.255
Openness by Treatment Group		-0.17 (0.11)	.132
Agreeableness by Treatment Group		0.01 (0.10)	.904
Conscientiousness by Treatment Group		0.01 (0.11)	.928

* p-value < .10; ** p-value < .05

MBDRS = Modified Blessed Dementia Rating Scale; LEQ = Lifetime of Experiences Questionnaire;

CAM = Confusion Assessment Method

The results for effects on the Attention outcome demonstrate several significant main effects: higher age was associated with higher attention scores; the effect of MBDRS (dementia severity) for the treatment group only such that lower MBDRS scores (indicating lower levels of impairment) were associated with higher attention scores in this group; the effect of LEQ (cognitive reserve) such that higher LEQ scores (indicating higher cognitive reserve) were associated with higher attention scores in both groups; and the effect of the CAM (delirium) such that lower CAM scores (indicating fewer delirium features) were associated with higher attention scores in both groups. Significant main effects of the personality variables were also seen such that lower extraversion scores in the control group and lower openness scores in the treatment group were associated with higher attention scores. The effects of higher agreeableness scores in the treatment group and lower conscientiousness scores in the control group approached significance. There were no significant interaction effects for the personality variables, indicating no significant moderating effects of personality on the association between treatment group and attention.

Table 4.7. *Moderating Effects of Personality on the Association between Treatment Group and Memory*

Effect		Estimate (Std Error)	p-value
Treatment Group Comparison		-0.35 (0.45)	.438
Baseline Covariates			
Age		-0.06 (0.04)	.140
Gender		0.50 (0.27)	.063*
ApoE ε4		-0.84 (0.45)	.063*
MBDRS	Control	0.28 (0.14)	.052*
	Treatment	0.04 (0.10)	.685
LEQ	Control	0.02 (0.03)	.585
	Treatment	0.03 (0.02)	.196
Time-Dependent Covariate			
CAM	Control	-0.21 (0.12)	.072*
	Treatment	-0.11 (0.10)	.257
Main Effects of Personality			
Neuroticism	Control	0.04 (0.04)	.393
	Treatment	0.05 (0.03)	.091*
Extraversion	Control	-0.08 (0.04)	.023**

Effect		Estimate (Std Error)	p-value
Openness	Treatment	-0.06 (0.03)	.049**
	Control	0.04 (0.04)	.201
Agreeableness	Treatment	-0.02 (0.03)	.594
	Control	-0.00 (0.04)	.974
Conscientiousness	Treatment	0.09 (0.03)	.007**
	Control	-0.02 (0.04)	.596
	Treatment	-0.03 (0.04)	.466
Moderators			
	Neuroticism by Treatment Group	0.01 (0.05)	.836
	Extraversion by Treatment Group	0.02 (0.05)	.692
	Openness by Treatment Group	-0.06 (0.05)	.202
	Agreeableness by Treatment Group	0.09 (0.05)	.078*
	Conscientiousness by Treatment Group	-0.01 (0.06)	.821

* p-value < .10; ** p-value < .05

MBDRS = Modified Blessed Dementia Rating Scale; LEQ = Lifetime of Experiences Questionnaire;
CAM = Confusion Assessment Method

The above results for effects on the Memory outcome demonstrate no significant main effects, although gender, ApoE ϵ 4, MBDRS (control group only), and CAM (control group only) approached statistical significance as follows: female gender, lower number of ApoE ϵ 4 alleles, higher MBDRS scores (indicating higher levels of impairment) in the control group, and lower CAM scores (indicating fewer delirium features) were associated with higher memory scores. Several main effects of personality variables were seen including: higher neuroticism scores associated with higher memory scores in the treatment group only (approached statistical significance); significant effects of lower extraversion scores on higher memory scores in both groups; and a significant effect of higher agreeableness scores on higher memory scores in the treatment group only. There was a statistically significant moderating effect of agreeableness on the association between treatment group and memory such that higher agreeableness scores were associated with higher memory scores in the treatment group.

Table 4.8. *Moderating Effects of Personality on the Association between Treatment Group and Orientation*

Effect		Estimate (Std Error)	p-value
Treatment Group Comparison		0.23 (0.45)	.614
Baseline Covariates			
Age		-0.06 (0.05)	.206
Gender		0.12 (0.29)	.683
ApoE ε4		-0.46 (0.51)	.371
MBDRS	Control	-0.12 (0.17)	.459
	Treatment	-0.26 (0.14)	.062*
LEQ	Control	0.02 (0.03)	.510
	Treatment	0.01 (0.03)	.776
Time-Dependent Covariate			
CAM	Control	-0.22 (0.09)	.014**
	Treatment	0.05 (0.09)	.570
Main Effects of Personality			
Neuroticism	Control	-0.03 (0.05)	.577
	Treatment	0.00 (0.03)	.924
Extraversion	Control	-0.02 (0.03)	.581
	Treatment	-0.06 (0.03)	.080*
Openness	Control	0.07 (0.04)	.048**
	Treatment	-0.01 (0.03)	.821
Agreeableness	Control	0.02 (0.04)	.580
	Treatment	0.03 (0.04)	.387
Conscientiousness	Control	0.00 (0.03)	.898
	Treatment	-0.06 (0.04)	.014**
Moderators			
Neuroticism by Treatment Group		0.03 (0.06)	.619
Extraversion by Treatment Group		-0.04 (0.04)	.300
Openness by Treatment Group		-0.08 (0.05)	.127
Agreeableness by Treatment Group		0.01 (0.06)	.853
Conscientiousness by Treatment Group		-0.06 (0.05)	.256

* p-value < .10; ** p-value < .05

MBDRS = Modified Blessed Dementia Rating Scale; LEQ = Lifetime of Experiences Questionnaire; CAM = Confusion Assessment Method

The above results for effects on the Orientation outcome demonstrate the significant main effect of the CAM (delirium) such that lower CAM scores (indicating fewer delirium features) were associated with higher orientation scores in the control group only. Additionally, the effect of

MBDRS in the treatment group approached statistical significance such that lower MBDRS scores (indicating lower levels of impairment) were associated with higher orientation scores. The main effect of extraversion approached significance and the effect of conscientiousness was significant in the treatment group such that lower scores were associated with higher orientation scores. There were no significant interaction (moderating) effects for the personality variables.

Table 4.9. *Moderating Effects of Personality on the Association between Treatment Group and Executive Function*

Effect		Estimate (Std Error)	p-value
Treatment Group Comparison		5.60 (1.57)	.000**
Baseline Covariates			
Age		-0.24 (0.16)	.121
Gender		-0.54 (1.09)	.623
ApoE ε4		-2.29 (1.96)	.242
MBDRS	Control	-1.14 (0.56)	.042**
	Treatment	-1.33 (0.51)	.009**
LEQ	Control	0.24 (0.13)	.062*
	Treatment	0.09 (0.11)	.451
Time-Dependent Covariate			
CAM	Control	-1.11 (0.47)	.017**
	Treatment	-0.56 (0.43)	.191
Main Effects of Personality			
Neuroticism	Control	0.06 (0.18)	.745
	Treatment	0.01 (0.14)	.917
Extraversion	Control	-0.07 (0.09)	.482
	Treatment	-0.31 (0.11)	.004**
Openness	Control	-0.04 (0.13)	.743
	Treatment	0.00 (0.13)	.982
Agreeableness	Control	0.17 (0.14)	.220
	Treatment	0.05 (0.11)	.677
Conscientiousness	Control	-0.12 (0.07)	.101
	Treatment	-0.02 (0.14)	.869
Moderators			
Neuroticism by Treatment Group		-0.04 (0.22)	.847
Extraversion by Treatment Group		-0.24 (0.13)	.064*
Openness by Treatment Group		0.04 (0.19)	.813
Agreeableness by Treatment Group		-0.12 (0.19)	.512
Conscientiousness by Treatment Group		0.10 (0.18)	.576

* p-value < .10; ** p-value < .05

MBDRS = Modified Blessed Dementia Rating Scale; LEQ = Lifetime of Experiences Questionnaire;
CAM = Confusion Assessment Method

The above results for effects on the Executive Function outcome demonstrate several significant main effects: the effect of MBDRS (dementia severity) such that lower MBDRS scores (indicating lower levels of impairment) were associated with higher executive function scores in both groups; the effect of the CAM (delirium) such that lower CAM scores (indicating fewer delirium features) were associated with higher executive function scores in the control group only; and, lower extraversion scores were associated with higher executive function scores in the treatment group only. Additionally, the effect of LEQ in the control group approached statistical significance such that higher LEQ scores (indicating higher cognitive reserve) were associated with higher executive function scores. There was a statistically significant moderating effect of extraversion on the association between treatment group and executive function such that lower extraversion scores were associated with higher executive function scores in the treatment group.

Aim 2: Test the effects of personality traits on engagement in the intervention during a period of acute cognitive decline.

Table 4.10 displays the results of the mixed-effects linear model used to test the effects of the five personality traits on engagement in the intervention. Total daily engagement was operationalized as the number of minutes engaged in the intervention multiplied by the level of participation. Since this analysis was conducted with the treatment group only, personality traits were included as main effects rather than interaction effects in this analysis.

Table 4.10 *Effects of Personality on Engagement in the Intervention (n=37)*

Effect	Estimate (Std Error)	p-value
Baseline Covariates		
Age	1.37 (1.75)	.442
Gender	17.5 (10.5)	.111
ApoE ϵ 4	55.34 (13.95)	.001**
MBDRS	1.44 (3.48)	.684
LEQ	0.58 (0.82)	.485
Time-Dependent Covariate		
CAM	0.81 (2.62)	.758
Personality Variables		
Neuroticism	0.42 (0.74)	.575
Extraversion	-0.19 (0.84)	.822
Openness	-1.86 (0.86)	.042**
Agreeableness	3.45 (0.86)	.001**
Conscientiousness	-2.38 (1.03)	.031**

* p-value < .10; ** p-value < .05

MBDRS = Modified Blessed Dementia Rating Scale; LEQ = Lifetime of Experiences Questionnaire; CAM = Confusion Assessment Method

The above results demonstrate several significant main effects: the effect of ApoE ϵ 4 such that higher numbers of ϵ 4 alleles were associated with greater engagement; lower openness scores were associated with greater engagement; higher agreeableness scores were associated with greater engagement; and, lower conscientiousness scores were associated with greater engagement.

Chapter 5

Discussion

Summary of Significant Findings

The purpose of this study was to explore whether personality moderated cognition-focused intervention outcomes in individuals at high risk for accelerated cognitive decline, and additionally, whether personality was associated with engagement in the intervention. Significant moderating effects of personality traits were found with regard to two cognitive outcomes: agreeableness moderated the memory outcome, and extraversion moderated the executive function outcome. Individuals with higher agreeableness were more likely to have improved memory outcomes, and those with lower extraversion were more likely to have improved executive function outcomes, as a result of the cognition-focused intervention. Additional significant main effects of personality were also identified which are important to consider given the exploratory nature of this study as well as the paucity of existing literature examining the effect of personality on cognition-focused intervention outcomes. Lower openness, higher agreeableness, and lower conscientiousness were significant predictors of increased engagement in the intervention. It is important to note that among the four cognitive outcomes examined, executive function was the only one that demonstrated a significant ($p=.000$) treatment effect in this sample. The other cognitive outcomes showed no significant improvement related to the cognition-focused intervention.

Moderating Effects of Personality on Cognitive Outcomes

Personality is known to influence activity preferences (Caspi, et al., 2005; Friedman, 2000), motivation for participation (Judge & Ilies, 2002), and performance (Elmstahl, et al., 1996). The influence of personality on activity participation among individuals with dementia has also been demonstrated (N. L. Hill, et al., 2010; Kolanowski, Buettner, Litaker, & Yu, 2006; Kolanowski, Litaker, Buettner, et al., 2011). In an RCT, the treatment effect of the population does not necessarily apply to any particular person or

subgroup (such as males vs. females), but rather represents the average effect across all individuals in the population (Kraemer, et al., 2006). Examining moderating effects, in this case personality traits, may help to identify whether a cognition-focused intervention for older adults at high risk for cognitive decline is differentially effective for individuals with certain personality characteristics. The study results identified statistically significant moderating effects for the memory and executive function outcomes, indicating that personality traits, in part, differentially influenced the effectiveness of the intervention for some participants. The following discussion will address the findings, both significant and non-significant, regarding the moderating effects of personality on the cognitive outcomes of the intervention. In addition, significant main effects of personality traits on the outcomes are discussed.

Moderating Effects of Extraversion on Intervention Outcomes. Across all cognitive outcome measures, extraversion displayed the most consistent pattern of significant effects. High extraversion is associated with sociability, preference for excitement and stimulation (McCrae & Costa, 2010), as well as improved rehabilitation outcomes (Elmstahl, et al., 1996); however, in every case of a significant main or interaction (moderating) effect, extraversion was negatively associated such that lower extraversion scores were associated with higher scores on the cognitive outcomes. Extraversion demonstrated a significant ($p=.064$) moderating effect on the executive function outcome such that individuals with lower extraversion scores benefitted more from the cognition-focused intervention. In other words, introverts were more likely to improve their executive function as a result of the treatment. Additionally, lower extraversion scores predicted higher attention scores in the control group ($p=.037$), higher memory scores in both groups ($p=.023/.049$), and approached statistical significance in predicting higher orientation scores in the treatment group ($p=.080$).

While much attention is typically focused on the characteristics of extraverts (assertive, active, talkative), introverts can be more difficult to characterize. McCrae & Costa (2010) explain that introversion should be viewed as the absence of extraversion rather than its opposite; introverts are

reserved but not unfriendly, even-paced rather than slow, and do not necessarily experience social anxiety. Among older adults with dementia, introverts have been found to be more likely to engage in one-on-one compared to group activities, although they engage for shorter periods of time (Kolanowski & Richards, 2002). All activities delivered in the RESERVE-DSD intervention were one-on-one between the participant and the research assistant. Interestingly, extraversion did not predict engagement in the intervention, so although introverts tended to experience better executive function outcomes as a result of the intervention, this was not a result of longer time on task or level of participation in the activity.

Two recent studies utilizing data from a randomized clinical trial of older adults (n=602) examined the role of extraversion in cognitive functioning over time and as a moderator of associations between ApoE genotype and cognition (B. Chapman, et al., 2012; Dar-Nimrod, et al., 2012). Chapman et al. (2012) assessed personality at baseline and cognitive function using the MMSE every six months for seven years and found that higher extraversion scores were associated with worse overall cognitive functioning over time. Using the same sample, Dar-Nimrod et al. (2012) explored whether personality traits (including extraversion) moderated the association of ApoE (presence or absence of E4 alleles) with overall cognitive function as well as the development of AD over a 6.5 year period. Extraversion was found to moderate the association between ApoE ϵ 4 and both cognitive outcomes: the risk for decreased cognitive function as a result of ApoE ϵ 4 alleles was much worse with higher extraversion compared to lower extraversion. The authors suggest that more extraverted people receive cognitive activity primarily through social interactions, the opportunities for which tend to decline in old age due to the loss of social networks as physical functioning deficits. Therefore, as older extraverts reduce their social activity, a primary source for their building of cognitive reserve through cognitive activity, the effect of ApoE ϵ 4 in decreasing cognitive reserve is expressed to a greater extent, or “unmasked”. Lower extraversion has also been associated with better driving performance among older adults (Adrian, Postal, Moessinger, Rasle, & Charles, 2011). However, this area of research is truly in its infancy. Much

is yet to be understood regarding the role of extraversion in treatment outcomes among older adults, particularly those with cognitive impairments, and how personality traits interact with other factors including biological (e.g., ApoE) and psychosocial (e.g., cognitive lifestyle) contributors to cognitive reserve.

Moderating Effects of Agreeableness on Intervention Outcomes. Agreeableness was found to have a significant moderating effect on memory ($p=.078$) such that individuals with higher agreeableness scores benefitted to a greater extent from the intervention. The direction of this effect is intuitive based on the description of agreeableness as describing one's tendency toward cooperation versus competition (McCrae & Costa, 1996). Agreeable individuals are eager to help others and tend to believe others are honest and well-intentioned (McCrae & Costa, 2010). These tendencies would favor participation in the activity intervention, and therefore benefit from it. Indeed, participants with higher agreeableness scores had significantly higher ($p=.001$) engagement in the intervention as well. Low agreeableness is also associated with aggressive behavior in dementia (Archer, et al., 2007; Whall, et al., 2008), which would likely negatively influence participation in and benefit from the intervention. Higher agreeableness also approached statistical significance ($p=.060$) as a predictor of higher attention scores in the treatment group. While these results suggest that more agreeable individuals may be better candidates for the intervention due to greater engagement as well as memory benefits, our previous work found that tailoring activity interventions to physical functional ability and individual interests may overcome some of the effects of low agreeableness (N. L. Hill, et al., 2010). This possibility has yet to be fully explored.

Moderating Effects of Openness on Intervention Outcomes. No significant moderating effects of openness were found for the cognitive outcomes. Lower openness was a significant ($p=.042$) predictor of higher engagement which was unexpected considering high openness is associated with adventurousness, problem solving, and exploring new compensatory responses (Costa, 1991) which

have been linked to improved functional outcomes (Duberstein, et al., 2003). It could be that the personalized selection of intervention activities to match participant preferences led to activities being perceived as familiar and comfortable to those with low openness scores. It is perhaps more likely, however, that the skewed distribution of openness scores in this study reflect an inherent problem in measurement, and therefore contributed to unexpected findings. Indeed, lower openness predicted ($p=.047$) higher attention scores in the treatment group, but higher openness predicted ($p=.048$) higher orientation scores in the control group. Results overall for this personality trait were divergent from expectations based on existing literature as well as inconsistent within the study results for different cognitive outcome measures.

It is quite possible that the measure of openness in this study was influenced by the use of an informant rating. Although the *NEO™-PI-3* is validated for use as an informant-based assessment, its developers acknowledge that observer ratings may show divergence from self-report ratings, likely due to differences in interpretation of individual items, different standards of comparison, or emphasis on particular aspects of a person (McCrae & Costa, 2010). Although these differences are typically small enough to preserve valid representations of personality overall, the trait of openness appears to be particularly vulnerable to difficulties with retrospective informant ratings. The distribution of openness scores in this sample was the most skewed of the five traits, with 64.3% of participants in the Low/Very Low categories. Extraversion had the next lowest percentage of Low/Very Low scores (45.1%), followed by neuroticism (29.5%), conscientiousness (19.8%), and agreeableness (15.9%). Historically, studies using an informant-based, retrospective personality measure for persons with dementia have found lower openness scores compared to relative norms (Duchek, Balota, Storandt, & Larsen, 2007; Kolanowski, Litaker, Buettner, et al., 2011). *NEO™-PI-3* items that measure openness include statements such as “Sometimes when reading poetry or looking at a work of art, he felt a chill or wave of excitement” and “He was intrigued by the patterns he found in art and nature.” These items were,

anecdotally, particularly difficult for informational subjects to answer. Retrospective, informant-based measurement of openness may be a challenge that has yet to be adequately addressed.

Moderating Effects of Conscientiousness on Intervention Outcomes. No significant moderating effects of conscientiousness were found for the cognitive outcomes. There were several main effects which were consistent in the direction of the effect: lower conscientiousness scores approached statistical significance ($p=.085$) as a predictor of higher attention scores in the control group, and were significant predictors of higher orientation scores in the treatment group as well as higher intervention engagement. In this sample, more highly conscientious individuals tended to participate to a lesser extent as well as exhibit lower scores on select cognitive outcomes, although significant moderating effects were not found. Conscientious individuals are determined, reliable, goal-oriented, and high achieving (McCrae & Costa, 2010). High conscientiousness is associated with health-protective behaviors leading to better functioning (Bogg & Roberts, 2004; Caspi, et al., 2005) and treatment success (Chou & Brauer, 2005; Ozer & Benet-Martinez, 2006), but these tendencies were not supported in this study. Although personality remains relatively stable over time, a recent systematic review of personality changes in AD found that conscientiousness was the trait most likely to change after a dementia diagnosis, with a systematic pattern of lower conscientiousness scores across studies (Robins Wahlin & Byrne, 2011). Premorbid personality assessments may have played a role in the ability to detect conscientiousness-specific moderating effects.

Another important consideration in interpretation of these findings is the cognitive status of the participants: older adults with mild to moderate dementia as well as delirium. Emerging evidence suggests that awareness of cognitive impairment among older adults may interact with conscientiousness and its effects on cognition-focused treatment outcomes (Werheid, Ziegler, Klapper, & Kuhl, 2010). Lack of awareness of cognitive impairment is common in dementia, ranging from 31% to 67% in those with mild to moderate AD (Leicht, Berwig, & Gertz, 2010; Orfei, et al., 2010), but some

individuals remain aware of their cognitive deficits even through later disease stages (Cosentino, Metcalfe, Butterfield, & Stern, 2007; Mayhew, Acton, Yauk, & Hopkins, 2001; Ownsworth, Clare, & Morris, 2006). This sample had an average CDR score of 1.3 (0.6) which ranged from 0.5 to 2.0, indicating a mild to moderate level of impairment. Conventional wisdom suggests that individuals with greater awareness of their impairment may be more motivated to participate in rehabilitation, which may in turn lead to better outcomes. However, Werheid, Ziegler, Klapper, & Kuhl (2010) examined motivation to participate in a cognition-focused intervention, awareness of impairment, and cognitive functioning in 32 older adults with MCI and 72 healthy controls. In contrast to controls, individuals with MCI who were more aware of their impairment were less motivated to participate in the cognitive intervention. Conscientious individuals are used to achieving goals and performing at a high level. If they are unable to perform a cognitive task to their own standards, and are aware of this decreased ability (such as cognitive impairment due to dementia or delirium), they may withdraw from or participate less in the activity. Some evidence suggests that highly conscientious individuals may use coping mechanisms such as denial when faced with the distress associated with lack of order and control due to cognitive impairment (Seiffer, Clare, & Harvey, 2005). It is possible that factors such as these played a role in the decreased intervention engagement of more conscientious individuals in this study, as well as the lack of moderating effects of conscientiousness on treatment outcomes.

Moderating Effects of Neuroticism on Intervention Outcomes. No significant moderating or main effects of neuroticism were found for the cognitive or engagement outcomes. Neuroticism refers to the general tendency to experience negative affects including fear, sadness, anger, and embarrassment (McCrae & Costa, 2010). High neuroticism is often implicated in negative outcomes including decreased motivation (Judge & Ilies, 2002), medication non-adherence (Hurtz & Donovan, 2000), psychological distress, and maladaptive coping strategies (McCrae & Costa, 2010), but this relationship is likely a complex one (Kern & Friedman, 2011). In some individuals, high neuroticism may

lead to increased attentiveness to health-related needs rather than anxiety and worry (Friedman, 2000; Friedman, et al., 2010), outcomes that may also depend on one's level of conscientiousness (Roberts, et al., 2009). Coupled with the tendency for this trait to increase over time among individuals with dementia (Robins Wahlin & Byrne, 2011), it may have been difficult to identify the moderating role of neuroticism for the intervention examined in this study.

Study Strengths and Limitations

Several limitations are important to consider in interpretation of study results. First is inherent to the nature of examining moderating effects which are included in statistical models as interaction terms. Although the study of moderating effects in RCTs has been championed by leaders in statistical methodology (Kraemer, et al., 2006) as well as the discipline of nursing specifically (J. A. Bennett, 2000), efforts to detect these effects are often unsuccessful due to insufficient statistical power (Shieh, 2009). The difficulty in detecting moderating effects has been described as "notorious", particularly in regard to studies with continuous predictor and moderator variables, as was the case with this study. The ability to detect statistically significant moderating effects for two of the five personality traits examined in this exploratory study is perhaps a testament to the pervasive influence of personality of treatment outcomes across populations and conditions; even given the limitations in statistical power with the relatively small sample size, moderating effects were still evident. However, the sample size as well as well-known difficulty in detecting significant moderating effects likely limited our ability to detect the full range of effects at play. Additionally, significant treatment effects were only found for one of the four cognitive outcomes measured (executive function). This may have limited our ability to detect the effect of a moderating variable on the treatment outcome as well.

Several measures utilized in this study also pose some limitations. First, the engagement measure, a combination of time spent on task in the intervention and the level of participation, was used in order to best characterize engagement with a single variable and also to maximize variability in

the measure. However, this variable was not without its drawbacks, primarily in regard to its ability to measure individuals at the extremes of the scale. Due to the data collection procedures implemented, we were unable to determine whether missing engagement data were due to subject refusals to participate, subject unavailability, or cognitive (delirium) state which prevented participation. Therefore, no zero values were included in the measures of this variable. Additionally, the maximum possible time on task was 30 minutes, which ultimately led to right-censoring of these data due to the fact that most (70.2%) of the intervention sessions were conducted for the maximum amount of time. In earlier work (N. L. Hill, et al., 2010), we noted this problem of consistently maximizing engagement time and the resultant limited variability in this measure. Previously, the activities examined were limited to 20 minutes, but this time was increased to 30 minutes in the present study. These results suggest that a still longer intervention time may be: 1) well-tolerated by those who consistently engage, and 2) necessary in order to accurately examine main and moderating effects on intervention engagement.

Other limitations related to study measures involve the cognitive outcomes. For the purposes of these analyses, the short-term and long-term recall items from the Montreal Cognitive Assessment were combined into one measure of memory. Although this provided for increased variability in this outcome and the ability to maintain parsimony in the statistical approach, it could also be argued that these two dimensions of memory are distinct and it may be more meaningful to consider them independently. It should also be noted that attention is a cognitive domain that is closely tied to delirium; one of its key is inattention (Inouye, 2006). In our analyses, in order to control for the daily fluctuations in cognitive function due to delirium, we included the daily delirium assessment measure (CAM) as a time-dependent covariate. Since the RESERVE-DSD intervention targeted attention, among other cognitive domains, by adjusting for CAM scores in the statistical analysis, we ran the risk of eliminating the effect of the intervention on the attention outcome.

Another limitation of this exploratory study was the inability to consider the effects of combinations of traits, or better still, complete personality profiles, for their potential moderating effects on the treatment outcomes. The critical importance of utilizing multiple personality characteristics as predictors of health outcomes was illustrated by Friedman & Booth-Kewley (1987). In their meta-analysis of hundreds of studies linking personality and disease, they illustrated that a particular set of personality characteristics increased the risk of disease and that multiple characteristics must be examined simultaneously in order to determine disease predictors. Utilizing valid multi-trait measurements of personality is considered a vital component of high quality personality and health research (Kern & Friedman, 2011); however, the exploratory nature of this study including its limited sample size prevented the examination of personality trait interactions.

Finally, this study has limited generalizability to the overall population of older adults with cognitive impairment. Individuals with dementia and delirium are known to be at high risk for future cognitive decline (Gross, et al., 2012), likely due to a lower level of retained cognitive reserve (Kolanowski, Fick, Clare, Therrien, et al., 2010). These characteristics make them a desirable group to study based on both clinical significance as well as the potential to observe cognitive changes (due to delirium resolution) in a shorter period of time. However, it is unknown whether or to what extent personality plays a role in delirium manifestation or resolution. The body of literature exploring the relationship between delirium and personality is scant at best. The few studies published have focused specifically on personality traits generally associated with psychopathology (Tully, et al., 2010), personality disorders and alcohol withdrawal-induced delirium (Nordstrom & Berglund, 1988), or published over 35 (Kornfeld, Heller, Frank, Edie, & Barsa, 1978) or even almost 80 years ago (Curran, 1934). Although the statistical analyses included the CAM as a time-dependent covariate to control for the fluctuating effect of delirium on cognitive outcomes, it is unknown to what extent the presence of delirium influenced potential moderating effects of personality traits on the intervention outcomes.

This study also had several notable strengths. First and foremost, it was conducted concurrently with the parent study: an ongoing, multi-site, randomized clinical trial (RESERVE-DSD). Use of the extensive data collected within the parent study allowed for control of multiple sources of extraneous variance in the statistical analyses, such as both genetic and psychosocial contributors to cognitive reserve, which would typically not be possible in an exploratory study. Additionally, the multiple measures for each outcome of interest (up to 30 days for each participant) allowed for the consideration of moderating effects over the treatment period rather than at a single post-test measurement. Multiple measurements on the same individuals can also improve statistical power without increasing the sample size (Shadish, et al., 2002). The application of a sophisticated statistical model is another strength of this study. The mixed effects linear model includes both fixed effects (those manipulated by the researcher) and random effects (those sampled from a larger population) (Ott & Longnecker, 2001). The models used were particularly appropriate due to their ability to analyze multi-level data (repeated measures on the same individuals over time) and to accommodate the unbalanced data inherent to the study design.

Implications and Recommendations for Future Research and Practice

This study was exploratory in nature and therefore does not provide confirmatory evidence regarding the role of personality in cognition-focused interventions for older adults with cognitive impairment. However, it does provide further support for the pervasive influence of personality on treatment outcomes as well as future directions for both nursing research and practice.

The consideration of moderating influences in cognition-focused intervention research is notably absent in the empirical evidence. Within nursing science specifically, it has been recommended that moderators be considered to determine the circumstances in which a nursing intervention provides the best outcome (J. A. Bennett, 2000), and this study begins to address that gap. Even in light of the limitations of this study as previously described, the personality traits of extraversion and agreeableness were found to moderate cognitive outcomes of the RESERVE-DSD intervention. Additionally, openness,

agreeableness, and conscientiousness were significant predictors of intervention engagement.

Personality traits are known to influence a wide variety of health and treatment outcomes (e.g., Bogg & Roberts, 2004; Conner, et al., 2007; de Bruijn, et al., 2009; Judge & Ilies, 2002), and their role in cognition-focused interventions for individuals with dementia and delirium appears to be no exception. While much remains to be understood concerning the complex interactions between personality traits and the myriad of other personal characteristics which may moderate cognition-focused intervention outcomes for individuals at high risk for cognitive decline, the consideration of personality in further development of these interventions and the studies to test them is warranted.

Future research on the moderating influence of personality on cognition-focused outcomes should begin with a larger-scale study to extend and explicate the results found here. Certainly, a larger sample size is necessary in order to explore interactions between different personality traits. A more holistic view of personality which considers multiple aspects of the individual is likely to be the most meaningful, both to researchers interpreting study findings as well as to clinicians and those receiving treatment. Sample characteristics in future studies should also be considered, and specifically dementia stage and presence or absence of delirium. Selecting participants in a more narrow range of dementia stage, such as early-stage only, would provide for clearer distinction regarding generalizability and also help to address concerns regarding personality change in certain traits throughout the course of dementia. Additionally, examining the role of personality in delirium and the outcome of delirium-focused interventions is a greatly needed addition to the scientific literature; however, this should be examined in a group of older adults with no dementia in order to clearly examine the factors involved.

Identifying the best candidates for a particular treatment provides for targeting of that treatment, and effect size in future research may be maximized. This may be a critical research area considering the current state of cognition-focused intervention evidence in order to account for a portion of the variability in results across studies (Aguirre, et al., 2013; Woods, et al., 2012). In a truly

personalized approach to treatment, the best option for each particular individual should be considered, rather than what may be best for a population of people, on average. Determining moderators of treatment effects provides a way to begin making these determinations.

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Appendix A

RESERVE-DSD Intervention Protocol

Innovation for DSD- Intervention Training Program

Drs. Ann Kolanowski and Linda Clare

Day 1

- **Welcome and Overview of Project**
- **Dementia and Delirium- what these conditions are - what to expect when you work with individuals who have DSD**
- **Communicating with participants who have Dementia and Delirium**
- **Communicating with family members who may be stressed by the changing health status of the participant**
- **Confidentiality**
- **Safety Issues when working with older adults who have dementia- fall and fatigue prevention**

Day 2

- **Benefits of using cognitive activities**
- **Demonstration and return demonstration on implementing activities one on one and cuing techniques (Least Restrictive Prompts).**
- **Data Collection Training:**
 - Engagement Rating Form: Time on Task and Level of Participation**
 - Activity Form**

Training Session and Protocol for Implementing Cognitively Stimulating Recreational Activities

Cognitive stimulation is a non-regimented intervention that promotes cognitive processing in order to facilitate neural plasticity and restore cognitive reserve. In this study, cognitive stimulation is provided by using stimulating recreational activities that encourage cognitive processing in the cognitive domains affected by delirium: attention, orientation, memory, abstract thinking and executive functioning. Our goal in this project is to promote cognitive processing so that delirium is resolved. Some examples of the activities we will use are: connect the dots, finish the phrase, name that tune. While the activities themselves are simple and easy to implement, they take considerable planning and organization by the Research Assistant to make sure they are delivered in a consistent fashion for each subject at each session.

There are several things you can do to help maximize the benefits our subjects receive from these activities. First, both the subject and the environment must be prepared for implementation of the intervention. During the intervention, one of the most important factors is using proper communication techniques with individuals who have DSD. We will review these principles and several others: active engagement, incremental increases in task difficulty; verbal encouragement and motivation throughout the session; feedback and praise; and variability in tasks. We will have one of our expert interventionists demonstrate how to implement cognitively stimulating recreational activities. We will practice in simulated session until you are comfortable and proficient in implementing cognitively stimulating recreational activities. We will also teach you how to scan the environment so that it supports engagement in activities.

1. Before you get started remember that each subject has their own list of prescribed activities and an order in which they are to be implemented over the 30 minute session. Consult this list every day for any possible changes. Activities are tailored to each subject's interests, abilities, and adjusted for problems with vision, hearing or language difficulties. Be sure you use the correct activities prescribed for each subject. Organize the activities you will use for each subject in the order they will be given (easy to hard). Use the activity cart to organize and transport activities. Principle: treatment fidelity and variability in tasks.
2. Scan the environment where you will conduct the activities to make sure it provides a good working space. Turn off TV, radio, pagers, cell phones and canned music unless specifically a part of the session. Adjust the lighting level so it is appropriate for the activities you will be doing. Ask nursing staff not to pass medications to subjects during the session. Request housekeeping not to clean the space during your scheduled session. The idea is to ensure that the environment will support engagement in cognitive activities and to head off distracting interruptions. Principle: control for extraneous factors that may affect the implementation of the intervention.
3. Once you enter the subject's room or the area where the session will take place-address the subject by their preferred name. Introduce yourself and sit down at their eye level. Be very cognizant of your non-verbal communication: smile and

- be pleasant in your manner. Let the subject know the purpose of the session and obtain their assent to proceed (“Mrs. Jones, I am here to work with you on some games and activities. Would you like to do that now?”). Proceed with assent. If the subject says “no”- wait one hour and return. If the subject refuses a second time- record the session on the activity form as a “refused” session. Principle: subject assent and proper communication technique.
4. Each subject should have time for needed bathroom visits prior to the intervention; glasses/hearing aides should be present; subjects should have proper footwear and be dressed appropriately for the session; and assistive devices such as cane/walker should be available. Principle: ensure that the subject is maximally receptive to the cognitive activities.
 5. Communicate using simple phrases, body language, gestures, and demonstration to promote understanding. Listen to the emotional expression of the individual, not simply the words. Do not interrupt when the individual is communicating. Principle: proper communication technique.
 6. Speak slowly- don’t shout! Shouting makes it more difficult for older adults to hear what you are saying because it raises the pitch of your voice. Principle: proper communication technique.
 7. Proceed with implementation in this fashion: After introducing yourself, begin session timing by activating the stop watch. Starting with the easiest level of task/exercise in the cognitive domain of attention, increase the level of difficulty as success occurs with the simpler task. For example: if the subject successfully counts to 10 (easy level), proceed to the moderate level and ask the subject to complete the Connect the Dots activity. If successful, go to the activity prescribed for the difficult level in the domain of attention. If at any point, the subject is not able to complete a task/exercise go on to the next cognitive domain and begin with an activity at the easy level, proceeding as described above. Attempt at least one task/exercise in each cognitive domain. The goal is to complete three activities (easy, moderate and hard) in each cognitive domain. Principle: treatment fidelity, incremental increases in task difficulty and variability in tasks.
 8. To initiate engagement in the activity use the System of Least Restrictive Prompts. Begin with verbal cueing (“Mrs. Jones, I’d like you to pick out all the items that are fruits in this picture”). If no response, follow with verbal cueing and demonstration of the activity (“For example, Here is an apple. Now you try it.”). This system is only used to begin activities. If the subject continues to not respond, proceed as in #10. Principle: proper communication technique.
 9. Work with each subject for 30 minutes or until he/she disengages from the activity. Disengagement is demonstrated by: the subject's dozing/falling asleep, negative remarks about the activity, turning away from the interventionist/activity, asking to leave, leaving or attempting to leave the area. You may attempt to re-engage a subject three times by verbally prompting them to continue with the task/exercise. After the third unsuccessful attempt stop the intervention. At the 30 minute point or after three unsuccessful attempts to re-engage the subject, select

- “stop” on the stop watch. Record the time on task, level of participation and the activities attempted for that session on the daily activity form. Principle: active engagement and treatment fidelity.
10. If the subject is too confused or refuses to initiate any activity, do not attempt the intervention at that time. Return approximately one hour later to attempt a second session. If the subject is still too confused to participate in the activities, do not attempt the intervention that day. Record zero minutes for time on task and either 0, 1 or 2 for level of participation, depending on the subject’s behavior. Principle: active engagement and treatment fidelity.
 11. Give subjects plenty of time to respond to the task/exercise (count to 5 before you ask a question again). To aid communication, use the same language you did the first time you asked the question or made a request – do not paraphrase. Principle: proper communication technique.
 12. Encourage subjects to do as much as possible independently. **Give cuing, as needed, however active involvement in the session is vital to improvement. Don’t provide subjects with the correct answer- the idea is to have the subject engage in cognitive activity that is sufficiently challenging to stimulate cognitive processing but not frustration.** Principle: active engagement and treatment fidelity.
 13. Praise often (feedback is very important- your praise is a reward!!). Principle: feedback and praise
 14. Encourage/ motivate subjects throughout the session (tell them: “you are doing well- keep going”) Principle: verbal encouragement and motivation
 15. Make the activity fun & interesting- let subjects know you are having a good time too- demonstrate your enjoyment by your non-verbal communication. Principle: verbal encouragement and motivation
 16. End the session by thanking subjects for their time and for an enjoyable afternoon. Reinforce how helpful they are to the project and let them know you will return the next day. Principle: proper communication technique.
 17. Record the time on task, level of participation and the activities attempted on the activity form. Principle: treatment fidelity
 18. If for any reason the intervention was not implemented according to this protocol, complete a manipulation checklist and indicated the reason(s) for protocol deviation. Principle: treatment fidelity.

Examples of Cognitive Interventions by Domain and Level of Difficulty

Domain	Level of Difficulty	Activity
Attention	Easy	<ol style="list-style-type: none"> 1. Recite the alphabet or count to 10 2. Sound Identification: Without allowing the subject to see what you are doing make various sounds for them to identify: Clapping hands, taping a pencil, tear paper, stomp on floor, bounce a ball, snap your fingers
	Moderate	<ol style="list-style-type: none"> 1. Dot to Dot (letters or numbers) 2. Song identification. Play short familiar songs to identify or use a sound effect CD (barking dog, meowing cat,, train, phone ringing, birds singing, rain, thunder etc) 3. In a paper bag, provide a variety of objects for subject to feel, identify and describe the texture. These materials should include some items familiar to subject: Sandpaper, fruit, cloth, feather, baking utensil etc.
	Difficult	<ol style="list-style-type: none"> 1. Word search sheets- using words from the subject's occupation, leisure activities, role function (ie mother, father) 2. Item search- search for familiar items embedded in a picture

Domain	Level of Difficulty	Activity
Orientation	Easy	3. Dot to Dot- (connecting both letters and numbers simultaneously)
		4. Concentration card game
		5. Find the Differences- show two similar pictures and identify the subtle differences
	Moderate	1. "Draw" number 8 in the air, one arm then the other. May continue by asking to draw other numbers or letters
		1. "Finger Math" Ask to show 4 fingers. Ask to show using both hands; ask to show using a different combination. Continue with other numbers.
		2. Maneuver toothpicks to form name or word selected by subject
Difficult	3. Calendar work: Give subject calendar, have subject identify the month, how many days, any holidays, etc.	
	4. Where am I: describe general places (I am crossing a busy street in a city with skyscrapers- where am I? I am sitting on sand and can see waves and feel the sun beating down on me- where am I?)	
	1. Pick-up sticks 2. Where am I? Describe specific places: I can see the Golden Gate bridge and trolley cars- where am I? I can see the White House and the Lincoln Memorial- where am I? 3. Map work Provide a local or state map. Have subject identify where they live and point	

Domain	Level of Difficulty	Activity
Memory	Easy	<p>out other places of interest such as parks, airports.</p> <ol style="list-style-type: none"> 4. Discuss current events from Newspaper. 5. Geometric/ plumbers puzzles 6. Build objects using blocks/bricks 7. Tiddly Winks
	Moderate	<ol style="list-style-type: none"> 1. Ask subject to identify how many times you clap your hands. Do this several times varying the number of times. 1. Show subject 3 common items such as a spoon, pen, keys. Place each item in a separate small brown bag. Have client place hand in the bag and identify the object from the feel of it. 2. Identify famous faces (movie stars, historical figures) 3. Bingo/ pokeno 4. Finish the Phrase
	Difficult	<ol style="list-style-type: none"> 1. Show a tray of 10 items for 1 minute. Subject to write down as many of the items as possible (Memory Tray) 2. Scavenger hunt

Domain	Level of Difficulty	Activity
Abstract Thinking	Easy	1. "Hand Pantomime" Have subject identify objects/actions you pantomime with your hand: spider, bird, writing, signaling stop, waving 2. Ink Spots- what does the design look like to you?
	Moderate	1. Abstract Picture- Have subjects add lines to initial figure to make a picture 2. Dominos 3. Low to high card game
	Difficult	1. Discuss current events from Newspaper 2. Discuss meaning of idioms, expressions and proverbs 3. Price is Right (arrange items (food, tools etc) in order of price) 4. Tiddly Winks 5. Discuss meaning of a poem
Executive Functioning	Easy	1. Give subject a category and have them verbally name 3 or more items in that category: fruit, pies, clothing, girls names etc; 2. Sort items by color/shape 3. Easy Pegboard games

Domain	Level of Difficulty	Activity
	Moderate	<ol style="list-style-type: none"><li data-bbox="814 358 1409 380">1. Make scrap book on a theme (cut outs from magazine)<li data-bbox="814 415 1409 436">2. Put pictures in correct sequence to tell a story<li data-bbox="814 472 1409 493">3. Calculate correct change for a purchase<li data-bbox="814 529 1409 550">4. Complete puzzle<li data-bbox="814 586 1409 607">5. Sewing cards<li data-bbox="814 643 1409 664">6. Needlecraft
	Difficult	<ol style="list-style-type: none"><li data-bbox="814 854 1094 875">1. "I Spy" Match game<li data-bbox="814 911 1094 932">2. Write a letter to a friend<li data-bbox="814 967 1094 989">3. Mind Teaser puzzles<li data-bbox="814 1024 1094 1045">4. Hangman<li data-bbox="814 1081 1094 1102">5. Wheel of Fortune<li data-bbox="814 1138 1094 1159">6. Cooking project<li data-bbox="814 1195 1094 1216">7. Build a Bird house

**Treatment Fidelity
(Completed by PD)**

Subject Code: _____

Date: _____

Time: _____

Interventionist _____

At the completion of the activity session, please evaluate the extent to which the activity was implemented according to protocol by answering the following questions:

1) Were today's activities the correct ones for this subject?

a. Yes ____

b. No ____

Explain:

2) Were activities given in the correct order (easy to hard in each domain)?

a. Yes ____

b. No ____

Explain:

3) Did the RA attempt to continue the intervention for 30 minutes?

a. Yes _____

b. No _____

4) Were there any extraneous/environmental circumstances that influenced the delivery of the intervention?

_____ a. Interference from staff, other residents, visitors, etc.

Explain:

_____ b. Subject uncooperative.

Explain:

_____ c. Subject ill.

Explain:

_____ d. Subject engaged in another activity.

Explain:

_____ e. Subject not available.

Explain:

_____ f. Environment not conducive to intervention: (lighting poor; background noise etc).

Explain:

5. Did the interventionist use the system of least restrictive prompts when attempting to engage the subject?

Yes _____ No _____
Explain:

6. Did the interventionist encourage and allow the subject to take an active part in the exercise/task?

Yes _____ No _____
Explain:

7. Did the interventionist praise the subject's success throughout the session?

Yes _____ No _____
Explain:

8. Did the interventionist use proper communication techniques with the subject?

Yes _____ No _____
Explain:

**Treatment Fidelity
(RA Interventionist)**

Subject Code: _____

Date: _____

Time: _____

Interventionist _____

At the completion of the activity session, please evaluate the extent to which the activity was implemented correctly by answering the following questions:

1) Was today's activity the correct one?

a. Yes ____

b. No ____

Explain:

2) Were there any extraneous circumstances that influenced the delivery of the activity?

_____ a. Inability of subject to stay by them self for independent activity.

Explain:

_____ b. Interference from staff, other residents, visitors, etc.

Explain:

_____ c. Subject uncooperative.

Explain:

_____ d. Subject ill.

Explain:

_____ e. Subject engaged in another activity.

Explain:

_____ f. Subject not available.

Explain:

_____ g. Interventionist not available.

Explain:

3. Were there any other circumstances that affected the implementation of activities today?

Yes ____ No

Explain:

4. Did you deviate from the established protocol for any reason?

Yes _____ No _____

Explain:

Appendix B
Study Instruments

MODIFIED BLESSED DEMENTIA RATING SCALE (MBDRS)

Subject Code _____

Date _____

Now I would like to ask you about (Patient's name)'s ability in everyday tasks during the past 6 months before hospitalization.

During the 6 months prior to hospitalization have you noticed any problem with (Patient name)'s ability.....

(REPEAT PROMPT FOR QUESTIONS 1-8)

During the 6 months prior to hospitalization have you noticed any problem with (Patient name)'s ability.....	0	1	2	7	8
1) to perform his/her usual household tasks?					
2) to cope with small sums of money?					
3) to remember a short list of items, such as a shopping list?					
4) to find his/her way indoors, either in his/her own home or in other familiar locations?					
5) to find his/her way around familiar streets, either on foot or when traveling by car?					
6) to grasp situations, or to recognize surroundings or people?					
7) to recall recent events, such as outings or visits?					
8) During the 6 months before this hospitalization, did you notice in (patient name) a tendency to dwell in the past?					

0 = No problem

1 = Some problem (e.g. sometimes, partial)

2 = Severe problem or inability

7 = Refused question

8 = Do not know

CLINICAL DEMENTIA RATING (CDR)

CLINICAL DEMENTIA RATING (CDR):	0	0.5	1	2	3
---------------------------------	----------	------------	----------	----------	----------

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home Appears too ill to be taken to functions outside a family home	
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

CONFUSION ASSESSMENT METHOD (CAM) WORKSHEET

Subject ID:

EVALUATOR:

DATE:

I. ACUTE ONSET AND FLUCTUATING COURSE

- a) Is there evidence of an acute change in mental status from the patient's baseline?
- b) Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go or increase and decrease in severity?

BOX 1

<input type="radio"/> YES	<input type="radio"/> NO
<input type="radio"/> YES	<input type="radio"/> NO
<input type="radio"/> YES	<input type="radio"/> NO

II. INATTENTION

Did the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what was being said?

III. DISORGANIZED THINKING

Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable, switching from subject to subject?

BOX 2

<input type="radio"/> YES	<input type="radio"/> NO
<input type="radio"/> YES	<input type="radio"/> NO

IV. ALTERED LEVEL OF CONSCIOUSNESS

Overall, how would you rate the patient's level of consciousness?

- Alert (normal)
- Vigilant (hyperalert)
- Lethargic (drowsy, easily aroused)
- Stupor (difficult to arouse)
- Coma (unarousable)

Do any checks appear in this box?

Positive for full delirium per CAM (based on above CAM)

- YES
- NO

****If all items in Box 1 are checked and at least 1 item in Box 2 is checked a diagnosis of delirium is suggested. They have to have both items 1 and 2 present and either 3 or 4***

Positive for subsyndromal delirium if 2 items are checked (Marcantonio et al., 2005 J Am Geriatr Soc)

- YES
- NO

Please indicate Delirium Subtype Below**

- Hyperactive
- Hypoactive
- Mixed

*Adapted from Inouye, SK et al Clarifying Confusion: The Confusion Assessment Method. A New Method for Detection of Delirium. *Ann Intern Med.* 1990; 113: 941-8

**Subsyndromal delirium from Yang et al., 2009 Psychosomatics. 50 (3): 248-254.

BASELINE MEDICAL CHART REVIEW

Subject Code: _____ Today's Date _____

Data to be extracted from patient medical chart:**Age:** _____**Gender:**

Female

Male

Race/ethnicity :

African American

American Indian

Asian

Caucasian

Latino

Other (please specify):

Marital Status:

Married

Widowed

Single, never married

Separated/Divorced

List all medical diagnoses**List all prescribed medications (regular & prn)** _____**List all prescribed therapies**

Physical Therapy

Occupational Therapy

Speech Therapy

Other (please specify): _____

Medical activity order (ie, bedrest, OOB etc) _____

Charlson Weighted Index of Co-morbidity

Assigned weighted for diseases	Conditions
1	Myocardial infarct Congestive heart failure Cerebrovascular disease Dementia Chronic Pulmonary disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2	Hemiplegia Moderate or severe renal disease Diabetes/end organ damage Any tumor Leukemia Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor AIDS

Assigned weights for each condition that a patient has. The total equals the score.
 Example: chronic pulmonary (1) and lymphoma (2), plus dementia (1) = (4).
 (Charlson, Pompei, Ales & MacKenzie, 1987)

Assigned score: _____

*Genome Core Facility
Huck Institute
The Pennsylvania State
University
210 Wartik Bldg
University Park PA 16802*

Collecting Mouth Cells

Your pack contains: 1 tube containing storage liquid
10 cotton wool swabs

As with all small objects and undrinkable liquids, please keep out of the reach of children

How to use the Cotton Wool Swabs

1. Each time you use the swabs, try to use half of the swabs (5) to rub inside the left part of the mouth and the other half (5) to rub inside the right part of the mouth.
2. The best way to collect the mouth cells is by rubbing the cotton wool swab along the inside of the mouth, (including the cheek, lip and gums) with a little pressure against the mouth as you do so – turning the swab as you go. Try to do this for about 20 seconds with each swab. If this proves to be too long, please just do it as long as you can. It does not hurt at all, but it might tickle a little.
3. Each time a swab has been used, place it in the tube containing the storage liquid - cotton wool swab end downwards. There are 10 swabs to use in total and please try to use all of these if possible. Although we can manage with less try to use at least 5 swabs. Be sure to do the tube lid up tightly. The swabs should not be stored in a fridge, but kept at room temperature and out of direct sunlight.
4. The best time to collect mouth cells is the first thing in the morning before brushing the teeth. The mouth is probably full of loose cells etc. However, this can be impractical. If the swabs are used during the day,
 - a) Try to take them mid-morning or mid-afternoon as long as possible from eating or drinking.
 - b) Do not eat or drink anything directly before swabbing.
 - c) Avoid hot liquids, alcohol and mouth wash before swabbing.
 - d) Do not swab after brushing the teeth or smoking.

Valenzuela, M.J. & Sachdev, P. (2007). Assessment of complex mental activity across the lifespan: Development of the lifetime of experiences questionnaire (LEQ). *Psychological Medicine*, 37(7), 1015-1025.

The Lifetime of Experience Questionnaire (LEQ) **Adapted for Informants- with permission**

Please answer as accurately as possible – choose the option which most closely fits with (name of subject's) experience.

LEQ Questions YOUNG ADULTHOOD

The following questions apply to the time in (name of subject) life between 13 and 30 years of age.

Lifestage Specific

- I. How many years of high school (i.e., secondary school or grades after Year 6) did he/she complete?

- II. Did he/she gain an end of high school certificate (e.g., High School Diploma, GDE)?
No Yes

- III. Did he/she continue with any type of training or study after leaving school (between the ages of 13 to 30 years of age)?
No Yes

If Yes, please fill in the table below. If No, go to question IV.

Please specify what type(s) of training or study he/she attempted up until 30 years of age and for how long he/she was enrolled. Some categories are given below. If his/her experience is not covered by this list, please fill in the details under 'Other.'

Type of Course	Precise Course Name	Number of Years Enrolled	F/T or P/T?
Clerical Training			
Business Course			
Trade Apprenticeship			
Other Technical Course			
College Diploma			
University Undergraduate			
University Masters			
University PhD/ Doctorate			
Other Graduate Course			
Any other course?			

Valenzuela, M.J. & Sachdev, P. (2007). Assessment of complex mental activity across the lifespan: Development of the lifetime of experiences questionnaire (LEQ). *Psychological Medicine*, 37(7), 1015-1025.

Lifestage Non-specific

I. How often was he/she seeking a member of his/her family or friend during this time?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

II. How often was he/she practicing or playing a musical instrument?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

III. How often would he/she practice or develop an artistic pastime (e.g. drawing, painting, writing, acting)?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

IV. How often did he/she do any kind of physical exercise?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

V. How often did he/she read (material of any sort) for more than five minutes?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

VI. How often did he/she practice speaking a second language?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

VII. Did he/she travel to any of the following continents between the ages of 13-30?

Pacific Islands

Asia/Subcontinent

Latin/Central America

North America

Europe/former USSR

Africa

Middle East

VIII. Between the ages of 13 to 30 did he/she have any other pastime, hobby or special interest not mentioned in this questionnaire?

If so, please list:

Valenzuela, M.J. & Sachdev, P. (2007). Assessment of complex mental activity across the lifespan: Development of the lifetime of experiences questionnaire (LEQ). *Psychological Medicine*, 37(7), 1015-1025.

Lifestage Non-specific

I. How often was he/she seeing a member of their family or friend during this time?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

II. How often was he/she practicing or playing a musical instrument?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

III. How often would he/she practice or develop an artistic pastime (e.g. drawing, painting, writing, acting)?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

IV. How often did he/she do any kind of physical exercise?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

V. How often did he/she read (material of any sort) for more than five minutes?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

VI. How often would he/she practice speaking a second language?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

VII. Did he/she travel to any of the following continents between the ages of 30-65?

Pacific Islands

Asia/Subcontinent

Latin/Central America

North America

Europe/former USSR

Africa

Middle East

VIII. Between the ages of 30-65 did he/she have any other pastime, hobby or special interest not mentioned in this questionnaire?

If so, please list:

Valenzuela, M.J. & Sachdev, P. (2007). Assessment of complex mental activity across the lifespan: Development of the lifetime of experiences questionnaire (LEQ). *Psychological Medicine*, 37(7), 1015-1025.

XIV. Between the ages of 30-65 did he/she undertake any form of formal study.

Yes No

If YES, please indicate the precise nature on the list below:

Type of Course	Precise Course Name	Number of Years Enrolled	F/T or P/T?
Clerical Training			
Business Course			
Trade Apprenticeship			
Other Technical Course			
College Diploma			
University Undergraduate			
University Masters			
University PhD/ Doctorate			
Other Graduate Course			
Any other course?			

Valenzuela, M.J. & Sachdev, P. (2007). Assessment of complex mental activity across the lifespan: Development of the lifetime of experiences questionnaire (LEQ). *Psychological Medicine*, 37(7), 1015-1025.

LEQ Questions LATE LIFE

You will now be asked questions about the present phase of _____ life, beginning from when he/she retired OR from around 65 years of age (whichever came first).

Lifestage Specific

I. At what age did he/she retire (please indicate if not applicable)?:

II. Does he/she currently reside:

Alone With a partner With a friend With Family

III. Is he/she currently a member of any social clubs or groups?

No Yes

If YES, please indicate how many

IV. Does he/she do any charity or volunteer work?

No Yes

If YES, please indicate nature of activity

V. How often might he/she make an outing to see a family member, friend or group of friends?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

Valenzuela, M.J. & Sachdev, P. (2007). Assessment of complex mental activity across the lifespan: Development of the lifetime of experiences questionnaire (LEQ). *Psychological Medicine*, 37(7), 1015-1025.

VI. What types of events or entertainment has he/she undertaken in the past 2 months?

Please tick for each time he/she has attended each one:

- Movies
- Plays/Drama
- Pub/RSL Club
- Concert/Recital
- Special Performance
- Dancing
- Visiting Friends
- Sporting Event
- Other: Specify

VII. How would he/she spend a typical day?

Please circle any of the following activities if he/she undertakes them on a typical day:

- | | |
|---------------------------|------------------------------|
| Sleep/Nothing | Teaching |
| House Work | Volunteer Work |
| TV | Paid Work |
| Radio | Strategic Games |
| Listening to Music | (e.g., Chess, Bridge, Cards) |
| Walking | Helping friends/family |
| Gardening | Pet Care |
| Crosswords | Artistry |
| | Prayer/Religious Activity |
| Socializing | Playing Music |
| Writing | Learning Something New |
| Studying | Hobby/Pastime |
| Intellectual/Professional | Other: Specify |

Valenzuela, M.J. & Sachdev, P. (2007). Assessment of complex mental activity across the lifespan: Development of the lifetime of experiences questionnaire (LEQ). *Psychological Medicine*, 37(7), 1015-1025.

VIII. How does he/she usually acquire information about world and national events?

Circle as many as are relevant to him/her:

Doesn't seek information

Friends

TV

Radio

Newspapers

Magazines

Internet

Other: Specify

IX. What kind of material is he/she reading on a regular basis?

Circle as many as are appropriate:

Just what is needed to get by

Newspaper articles

Magazine articles

Novels

Fiction stories

Journals or Monographs

Non-Fiction Books

All of above

Other: Specify

Valenzuela, M.J. & Sachdev, P. (2007). Assessment of complex mental activity across the lifespan: Development of the lifetime of experiences questionnaire (LEQ). *Psychological Medicine*, 37(7), 1015-1025.

Lifestage Non-specific

I. How often was he/she seeing a member of their family or friend during this time?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

II. How often was he/she practicing or playing a musical instrument?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

III. How often would he/she practice or develop an artistic pastime (e.g. drawing, painting, writing, acting)?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

IV. How often did he/she do any kind of physical exercise?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

V. How often did he/she read (material of any sort) for more than five minutes?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

VI. How often would he/she practice speaking a second language?

Never Less than Monthly Monthly Every 2 weeks Weekly Daily

VII. Did he/she travel to any of the following continents between the ages of 65+?

Pacific Islands

Asia/Subcontinent

Latin/Central America

North America

Europe/former USSR

Africa

Middle East

Valenzuela, M.J. & Sachdev, P. (2007). Assessment of complex mental activity across the lifespan: Development of the lifetime of experiences questionnaire (LEQ). *Psychological Medicine*, 37(7), 1015-1025.

VIII. Since retiring OR the age of 65 (whichever came first), has he/she had any other pastime, hobby or special interest not mentioned in this questionnaire?

If so, please list:

IX. Since retiring OR the age of 65 (whichever came first), has he/she undertaken any form of formal study?

Yes No

If YES, please indicate the precise nature on the list below:

Type of Course	Precise Course Name	Number of Years Enrolled	F/T or P/T?
Clerical Training			
Business Course			
Trade Apprenticeship			
Other Technical Course			
College Diploma			
University Undergraduate			
University Masters			
University PhD/ Doctorate			
Other Graduate Course			
Any other course?			



CLOX: an executive clock drawing task

Donald R Royall, Jeffrey A Cordes and Marsha Polk

J. Neurol. Neurosurg. Psychiatry 1998;64;588-594
doi:10.1136/jnp.64.5.588

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CLOX: an executive clock drawing task

Donald R Royall, Jeffrey A Cordes, Marsha Polk

Abstract

Objective—To describe a clock drawing task (CLOX) designed to elicit executive impairment and discriminate it from non-executive constructional failure.

Subjects—90 elderly subjects were studied (45 elderly and well persons from the independent living apartments of a continuing care retirement community and 45 patients with probable Alzheimer's disease). The clock drawing performance of elderly patients was compared with that of 62 young adult controls.

Methods—Subjects received the CLOX, an executive test (EXIT25), and the mini mental state examination (MMSE). The CLOX is divided into an unprompted task that is sensitive to executive control (CLOX1) and a copied version that is not (CLOX2). Between rater reliability (27 subjects) was high for both subtests.

Results—In elderly subjects, CLOX subscores correlated strongly with cognitive severity (CLOX1: $r=-0.83$ v the EXIT25; CLOX2: $r=0.85$ v the MMSE). EXIT25 and MMSE scores predicted CLOX1 scores independently of age or education ($F(4,82)=50.7$, $p<0.001$; $R^2=0.71$). The EXIT25 accounted for 68% of CLOX1 variance. Only the MMSE significantly contributed to CLOX2 scores ($F(4,72)=57.2$, $p<0.001$; $R^2=0.74$). CLOX subscales discriminated between patients with Alzheimer's disease and elderly controls (83.1% of cases correctly classified; Wilkes' $\lambda=0.48$, $p<0.001$), and between Alzheimer's disease subgroups with and without constructional impairment (91.9% of cases correctly classified; Wilkes' $\lambda=0.31$, $p<0.001$).

Conclusions—The CLOX is an internally consistent measure that is easy to administer and displays good inter-rater reliability. It is strongly associated with cognitive test scores. The pattern of CLOX failures may discriminate clinical dementia subgroups.

(*J Neurol Neurosurg Psychiatry* 1998;64:588-594)

Keywords: dementia, Alzheimer's, executive, assessment

There is a growing interest in the potential of clock drawing tests (CDTs) as a screen for cognitive impairment.¹⁻⁷ CDTs have been found to correlate significantly with traditional cognitive measures^{1 2 4 5} and to discriminate healthy from demented elderly patients.⁸ The severity of clock drawing failures progresses over time in Alzheimer's disease, and correlates

with longitudinal changes in cognitive testing.^{5 9} Moreover, CDTs are rapid and well accepted.⁵

Unfortunately, CDTs still have both conceptual and practical limitations. Conceptually, clock drawing has been viewed as a visuospatial task, sensitive to right parietal pathology.¹⁰⁻¹² Recent studies undermine this notion, however. For example, CDT failure has been shown to be a state dependent feature of major depression.¹³ Whereas Alzheimer's disease may be associated with signs of right hemispheric impairment (visual agnosia and apraxia), major depression generally is not. Failures of CDTs in non-cortically impaired subjects undermine a chiefly visuospatial conceptualisation of the CDT.¹⁴

Practical limitations arise from the fact that there is no consensus regarding CDT rating. This is a problem because a patient's performance may vary greatly as a function of the task itself. Patients with Alzheimer's disease have been reported who can construct perfectly adequate copies of a clock face, yet are unable to draw a clock when given a blank piece of paper to work from.¹⁵ The available CDT rating schemes vary widely on the stimuli given to the subject, the time to which the clock is set, and the elements considered during scoring. Moreover, there are qualitative differences in how dementia subgroups fail a clock drawing task even if they are equated for overall severity of dementia.^{9 15} These qualitative differences must be acknowledged in scoring a CDT if it is not to be biased by the presentation of a single dementia syndrome.¹⁶

We propose that the concept of "executive control" has the potential to greatly improve CDT interpretation. Executive control functions (ECFs) guide complex goal directed behaviour in the face of novel, irrelevant, or ambiguous environmental cues.^{17 18} Examples of ECFs include goal selection, planning, motor sequencing, selective attention, and the self monitoring of a subject's current action plan. All are required by clock drawing. Impairment of ECF was added in 1994 to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition's definition of dementia.¹⁹

Neuropsychological test scores generally reflect the integrity of both the cognitive domain in question and its executive control. In the case of clock drawing, a subject's performance requires the separate analysis of visuoconstructional praxis and the executive control demanded by the testing paradigm. The relative variance in CDT performance explained by ECF remains to be determined. This is because (1) current CDT rating schemes are designed to elicit constructional

Department of
Psychiatry, University
of Texas, Health
Science Center at San
Antonio, Texas, USA
D R Royall
Jeffrey A Cordes
Marsha Polk

Department of
Medicine, South Texas
Veterans' Health
System, Audie L
Murphy Division,
Geriatric Research
Education Clinical
Center (GRECC)
D R Royall

Division of Clinical
Pharmacology
D R Royall

Correspondence to:
Associate Professor
D R Royall, Department of
Psychiatry, University of
Texas Health Science Center
at San Antonio, 7703 Floyd
Curl Drive, San Antonio,
Texas 78284-7792, USA.
Telephone 001 210 567
8545; fax 001 210 567 8509;
email: royall@uthscsa.edu

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Table 1 Mean (SD) for selected clinical variables by group

Variable	Young adult controls (n=62)	Independent living retirees (n=45)	Probable AD (n=45)	AD cases with MMSE constructional errors (n=19)	AD cases without MMSE constructional errors (n=26)
Age (y)	24.4 (4.3)	76.0 (11.6)*	75.8 (8.5)*	73.8 (9.2)*	76.5 (7.9)*
Education (y)	14.6 (1.2)	14.9 (2.2)	12.7 (2.8)* ***	13.4 (2.1)* ***	12.2 (3.1)* ***
EXIT25	4.2 (2.2)	8.8 (3.7)*	26.8 (7.5)* ***	31.1 (6.9)* ***	23.7 (6.3)***###
MMSE	29.3 (0.9)	29.1 (1.3)	16.4 (6.9)* ***	12.0 (6.7)* ***	19.7 (5.0)***###
CLOX1	13.2 (1.6)	12.1 (2.6)*	4.6 (4.5)* ***	2.1 (3.3)* ***	6.5 (4.4)***###
CLOX2	14.2 (1.2)	14.2 (1.0)	8.3 (5.3)* ***	3.4 (3.9)* ***	12.0 (2.4)***###

AD=Alzheimer's disease.

*P<0.05 v young adults.

***P<0.001 v well elderly cases.

###P<0.001 v patients with AD with MMSE constructional impairment.

failures rather than ECF related failures, (2) bedside mental status examinations are either indirectly sensitive to ECF failures or ignore them altogether, and (3) the possible qualitative differences in CDT failures arising from true constructional as opposed to ECF related pathology are not routinely assessed.²⁰ Although several authors have commented on the sensitivity of CDTs to "abstract" thinking or "complex behaviour", there have been no efforts to grade the CDT as an executive task, nor to divorce the executive control of clock drawing from drawing itself. We expect that a significant proportion of the variance in CDT failures is in fact the product of executive dyscontrol. In this paper, we describe a clock drawing task which has been designed specifically to discriminate executive and non-executive elements.

Methods

SUBJECTS

The CLOX instrument was first piloted in a sample of 62 young adult undergraduates (mean age 24.4 (SD 4.3) years) attending the University of Texas at San Antonio. This reference group was compared with 90 elderly subjects, selected from two clinical settings. Forty five were recruited from the independent living apartments of a large retirement community. All were free of depression and self reported impairment in activities of daily living. The mean geriatric depression scale (GDS short form)²¹ score was 1.2 (SD 1.5). Scores >07/25 are considered "depressed". The mean independent activities of daily living score for this group was 13.7 (SD 0.77). We further required that these cases scored no less than 1.0 SD below the mean for 25 year old subjects on both the verbal and performance subscales of the Weschler adult intelligence scale. This helps to assure us that the elderly control group is free of incipient dementias. Less than 25% of independent living septuagenarians at this retirement community can pass this stringent criterion. Informed consent was obtained before the evaluation of both control groups.

The remaining 45 elderly subjects were outpatients diagnosed with probable Alzheimer's disease using National Institute of Neurological Communicative Disorders and Stroke (NINCDS) criteria.²² All had undergone comprehensive geriatric assessments, including examination by a geropsychiatrist. Each received a history, physical examination, mental state examination, neu-

ropsychological testing, and functional status evaluation. Clinical data were confirmed by family members or other available caregivers. All pertinent laboratory results and neuroimaging studies were reviewed. The patients with Alzheimer's disease were further divided into those with (n=19) and those without (n=26) gross constructional impairment on the mini mental state examination (MMSE). Table 1 compares these groups on selected clinical variables.

INSTRUMENTS

Subjects were interviewed by trained physicians using the CLOX, EXIT25, and MMSE. The CLOX was scored blind to the other instruments. Each instrument is briefly described below.

The executive clock drawing task (CLOX)

The CLOX has been divided into two parts to help discriminate the executive control of clock drawing from clock drawing itself. The patient is first instructed to draw a clock on the back of the CLOX form (see fig 3). He or she is instructed only to "Draw me a clock that says 1:45. Set the hands and numbers on the face so that a child could read them." The instructions can be repeated until they are clearly understood, but once the subject begins to draw no further assistance is allowed. The subject's performance is rated according to the CLOX directions, and scored as "CLOX1".

CLOX1 reflects performance in a novel and ambiguous situation. The patient is presented only with a blank surface and no further guidance regarding the task. He or she is responsible for choosing the clock's overall form (a digital or analog face, alarm clock, wrist watch, or wall clock, etc), its size, position on the paper, elements (hands, numbers, date indicators), the forms of these elements (hands as arrows, relative lengths, roman v arabic numerals, etc). Furthermore, the patient must also initiate and persist in clock drawing through a sequence of constructional actions (usually drawing the outer circle, followed by placing the numbers if any, followed by setting the time). Finally, he or she must monitor progress as the task unfolds, both anticipating (placing the 12, 6, 3, and 9 first) and/ or correcting errors as they occur.

It is just as important to note what a patient *does not do* during a clock drawing task. Our CLOX form and its verbal instructions have been designed to distract the subject with

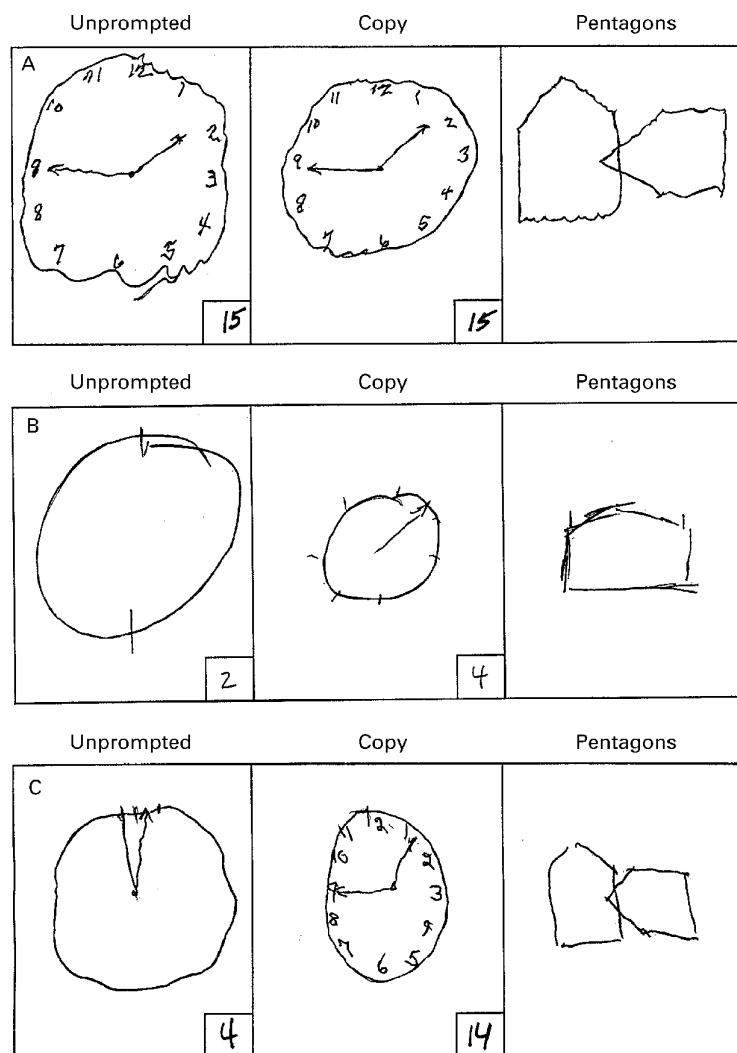


Figure 1 Qualitative differences in CLOX performance, in a normal elderly control, a patient with Alzheimer's disease, and a patient with non-cortical vascular disease. (A) An 82 year old elderly control. EXIT25=08/50 (scores >5/50 impaired), MMSE=29/30 (scores <24/30 impaired). (B) A 74 year old married white woman with Alzheimer's disease. EXIT25=21/50 (24/50 comparable with six; year old children or residents requiring skilled nursing), MMSE=12/30. (C) A 74 year old right handed white man with a history of coronary artery disease (status post myocardial infarction), hypertension, non-insulin dependent diabetes mellitus, and falls. EXIT22=24/50, MMSE=28/30.

strongly associated but irrelevant cues. The circle in the left lower corner is irrelevant to clock drawing when viewed from the reverse side of the form, but it tempts the patient to place their clock within its image. We chose the words "hand" and "face" because they are more strongly associated with body parts than clock elements, and may trigger semantic intrusions from their more common meanings. The number "45" does not appear on a typical clock face, and may intrude into the patient's construction in the form of a digital image (1:45) or hands pointing to the four or five

Table 2 Pearson product moment correlations for selected clinical variables

	Age	Education	EXIT25	MMSE	CLOX1	CLOX2
Education	0.05					
EXIT25	0.02	-0.40*				
MMSE	-0.05	0.39*	-0.92*			
CLOX1	-0.08	0.36*	-0.83*	0.82*		
CLOX2	-0.10	0.24*	-0.79*	0.85*	0.79*	

*P<0.05.

o'clock positions. CLOX scores range from 0–15. Lower scores reflect greater impairment.

The CLOX's second step is a simple copying task. The examiner allows the patient to observe him or her drawing a clock in the circle provided on the scoring sheet. The examiner sets the hands again to "1:45", places the 12, 6, 3, and 9 first, and makes the hands into arrows. The patient is allowed to copy the examiner's clock. This clock is scored as "CLOX2". The difference between CLOX scores 1 and 2 is hypothesised to reflect the specific contribution of executive control versus visuospatial praxis to overall clock drawing performance assessed by CLOX1. Assuming that right parietal cortical function has not been compromised, lesions to the frontal systems controlling clock drawing should affect CLOX1 more than CLOX2. This could occur in major depression, non-cortical dementias, or frontal type dementias that spare posterior cortical regions. If the right cortical hemisphere is affected, both scores should suffer.

Figure 1 presents the clock drawing performance of a non-demented elderly control versus two demented patients who have been matched to their overall level of executive control. Each patient's pentagon drawing from the MMSE²³ has been included for comparison. Note that the pentagons in the MMSE are essentially a copying task that depends little on executive control.

Patient A is an independent elderly control. The presence of an essential tremor does not affect CLOX scoring. Patient B has Alzheimer's disease. Clock drawing is impaired in both unprompted and copy conditions. The MMSE has an inherent bias towards cortical type dementia features.²⁴ This is reflected by impairment in patient B's MMSE pentagons and total MMSE score. Patient C has a vascular dementia without cortical features. Only the unprompted clock drawing task is affected. This patient's MMSE pentagons and total MMSE score is within that instrument's normal range.

THE EXECUTIVE INTERVIEW (EXIT25)

The EXIT25 is a bedside measure of executive control.^{25, 26} It defines the behavioural sequelae of executive dysfunction and provides a standardised clinical encounter in which they can be observed. EXIT25 scores correlate well with other measures of ECF including the Wisconsin card sort ($r=0.54$), trail making part B ($r=0.64$), the test of sustained attention (time, $r=0.82$; errors, $r=0.83$) and Lezak's tinker toy test ($r=0.57$). EXIT25 scores also seem to correlate strongly with mesiofrontal cerebral blood flow by single photon emission computed tomography (SPECT).²⁷

EXIT25 scores range from zero to 50. Higher scores suggest greater impairment. A cut off point of 15 out of 50 best discriminates non-demented elderly controls from both cortical and non-cortical dementing illness (SE=0.93, SP=0.83; area under receiver operating curve (ROC), $c=0.93$).²⁸ An EXIT25 cut off point of 10/50 best discriminates young adults with and without mesiofrontal perfusion

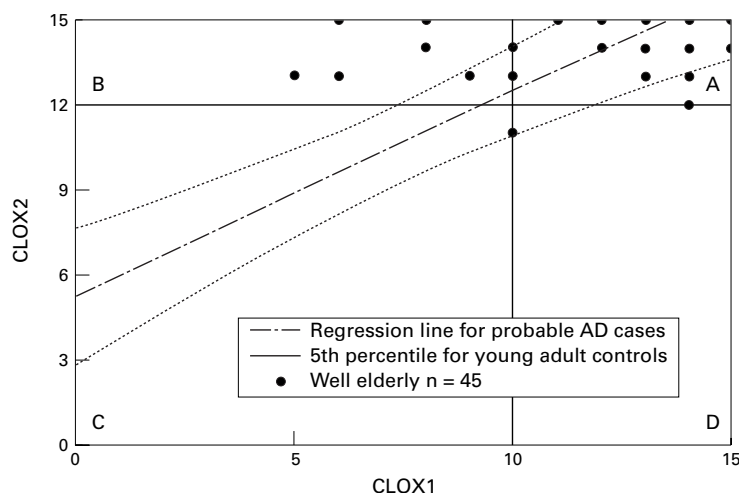


Figure 2 Scatterplot of CLOX1×CLOX2 scores for 45 independent and well elderly subjects. Regression line for 45 patients with probable Alzheimer's disease superimposed.

deficits after anterior cerebral artery aneurysmectomy.²⁷ The EXIT25 is more sensitive than the MMSE to early cognitive impairment and non-cortical dementia in elderly subjects.²⁴⁻²⁶

THE MINI MENTAL STATE EXAM (MMSE)

The MMSE is a familiar instrument.²³ It has been criticised for insensitivity in early dementia, and poorly educated subjects.²⁸ In our experience, the MMSE is also selectively biased against the detection of isolated frontal system disease.²⁴⁻²⁹ We hypothesise that in the absence of posterior cortical type constructional impairment, CLOX scores will be more sensitive to dementia than the MMSE. The MMSE was obtained blind to the subjects' EXIT25 and CLOX scores.

Results

RELIABILITY

The internal consistency of the CLOX in this sample was high (Chronbach's $\alpha=0.82$). Item total correlations ranged from $r=0.32$ to 0.77 (mean $r=0.41$). No item improved Chronbach's α if removed. The CLOX's between rater reliability was determined in a subset of 27 elderly subjects. The subjects' clocks were examined by two blind raters in the absence of clinical or demographic information. A high degree of between rater reliability was found (CLOX 1: $r=0.94$, CLOX 2: $r=0.93$; both $p<0.001$) (item 5 was excluded from this analysis).

CONSTRUCT VALIDITY

Scores for CLOX correlated strongly with cognitive impairment (EXIT25 and MMSE scores)(table 2). These instruments made significant contributions to CLOX1 scores after adjusting for age and education ($F(4,82)=50.7$, $p<0.001$; $R^2=0.71$). In a forward stepwise least squares regression model, the EXIT25 entered first, accounting for 68% of variance in CLOX1 scores (partial $R^2=0.68$). The MMSE entered next (partial $R^2=0.03$). Age did not contribute significantly to the model after adjusting for the EXIT25 and

MMSE. Education failed to enter. By contrast, only the MMSE significantly contributed to a similar model of CLOX2 scores ($F(4,72)=57.2$, $p<0.001$; $R^2=0.74$). It accounted for 72% of CLOX2 variance after adjusting for age and education. The EXIT25 failed to enter. Tolerance for these analyses was set to 0.15 to avoid possible multicollinearity.

The relative contributions of ECF (EXIT25) and constructional praxis to unprompted clock drawing (CLOX1) can be estimated by using CLOX2 scores as a proxy for constructional praxis. Together, the EXIT25 and CLOX2 explained 74% of the variance in CLOX1 scores ($F(2,86)=120.98$, $p<0.001$; $R^2=0.74$). The EXIT25 was responsible for 93% of the variance in CLOX1 scores (partial $R^2=0.69$).

DISCRIMINANT VALIDITY

We have examined the CLOX's ability to make two clinically important discriminations; firstly, between well elderly subjects and patients with Alzheimer's disease, and secondly, between Alzheimer's disease subgroups who present with and without gross constructional impairment. CLOX subscales discriminated Alzheimer's disease cases from elderly controls after adjusting for age, education, and MMSE test performance (MANCOVA: $R(2,81)=3.6$, $p<0.03$ (covarying age, education, and MMSE scores)). They did not discriminate these groups after adjusting for the EXIT25 ((MANCOVA: $R(2,85)=1.7$, NS) (covarying EXIT25 scores)).

In a discriminant model, the pattern of performance on the two CLOX subscales correctly identified 83.1% of cases (Wilkes' lambda = 0.48; $F(2,86)=46.27$, $p<0.0001$). For comparison, 89.9% of cases were correctly identified by the combination of the EXIT25 and the MMSE (Wilkes' lambda = 0.29; $F(2,86)=103.80$, $p<0.0001$).

However, patients with Alzheimer's disease are clinically heterogeneous. Specifically, Alzheimer's disease subgroups are known to exist that differ with respect to right hemispheric pathology.³⁰⁻³² Therefore, we used the qualitative evaluation of dementia (QED)²⁴ to divide the patients with Alzheimer's disease into those with (n=19) and without (n=26) grossly disorganised MMSE pentagrams, to see if CLOX subscales could discriminate between them. These Alzheimer's disease subgroups differed in their EXIT25 and MMSE scores (table 1). However, CLOX2 scores discriminated between these groups after adjusting for these measures ((ANCOVA): $F(1,33)=40.13$, $p<0.0001$ (covarying EXIT25 and MMSE scores)). CLOX1 scores did not (ANCOVA: $F(1,33)=0.61$, NS). This suggests (1) that the constructional differences between these Alzheimer's disease subgroups cannot be attributed solely to general differences in dementia severity, and (2) that this difference is selectively detected by the CLOX2 paradigm. In a discriminant model, the pattern of performance on CLOX1 × CLOX2 subscales correctly classified 91.9% of these Alzheimer's disease subgroups (Wilkes' lambda = 0.31; $F(2,34)=37.8$; $p<0.001$) This is remarkable

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CLOX: An Executive Clock Drawing Task[®]

STEP 1: Turn this form over on a light colored surface so that the circle below is visible. Have the subject draw a clock on the back. Instruct him or her to **“Draw me a clock that says 1:45. Set the hands and numbers on the face so that a child could read them.”** Repeat the instructions until they are clearly understood. Once the subject begins to draw no further assistance is allowed. Rate this clock (CLOX 1).

STEP 2: Return to this side and let the subject observe you draw a clock in the circle below. Place 12, 6, 3, & 9 first. Set the hands again to “1:45”. Make the hands into arrows. Invite the subject to copy your clock in the lower right corner. Score this clock (CLOX 2).

RATING			
Organizational Elements	Point Value	CLOX 1	CLOX 2
Does figure resemble a clock?	1		
Outer Circle Present?	1		
Diameter > 1 inch?	1		
All numbers inside the circle?	1		
12, 6, 3, & 9 placed first?	1		
Spacing Intact? (Symmetry on either side of the 12-6 axis?) If “yes” skip next.	2		
If spacing errors are present, are there signs of correction or erasure?	1		
Only Arabic numerals?	1		
Only numbers 1 - 12 among the Arabic numerals present?	1		
Sequence 1-12 intact? No omissions or intrusions.	1		
Only two hands present?	1		
All hands represented as arrows?	1		
Hour hand between 1 and 2 o'clock?	1		
Minute hand longer than hour?	1		
None of the following	1		
1) hand pointing to 4 or 5 o'clock?			
2) “1:45” present?			
3) intrusions from “hand” or “face” present?			
4) any letters, words or pictures?			
5) any intrusion from circle below?			
	TOTAL		

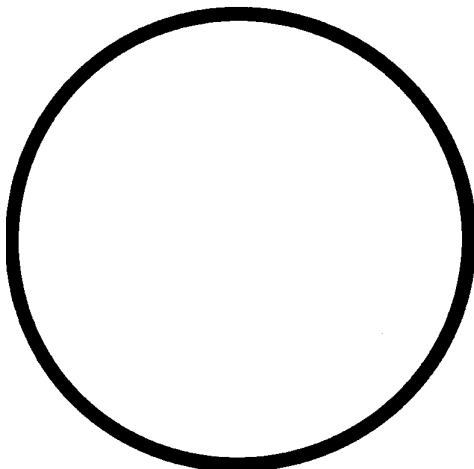


Figure 3

because the combination of EXIT25 and MMSE scores, which takes much longer (25–30 minutes) to administer, gave a less satisfactory performance (Wilkes' lambda =0.73; $F(2,34)=6.4$; $p<0.005$; 75.7% correctly identified).

INTERPRETING CLOX SCORES

CLOX scores were tightly distributed in young adult subjects (CLOX1 =13.2 (1.6); CLOX2 =14.2 (1.2) (table 1)). Thus, a CLOX1 score of 10/15, or a CLOX2 score of 12/15, represents the fifth percentile (2 SD below the mean) for the young adult reference group (fig 2). Cases presenting in box A of fig 2 have scored above the fifth percentile for young adult controls on both CLOX subscales. Cases in box B are below the fifth percentile for their unprompted CLOX1 score, but not the copied condition (CLOX2). Those in box D would have constructional > executive impairment.

Cases in box C have significant impairment relative to young adults on both CLOX subscales. The regression line for the 45 patients with NINCDS probable Alzheimer's disease enters this box from box A (fig 2). Cases presenting above this regression line have more executive impairment than would be expected for an average Alzheimer's disease case at that CLOX2 score. Cases presenting below this regression line would represent greater constructional impairment than could be expected for patients with Alzheimer's disease at similar CLOX1 scores. Figure 2 also presents the CLOX scores for the 45 elderly controls. It is immediately apparent that a significant fraction of this group (n=6, 14%) is presenting in box B (with relatively isolated executive impairment relative to both patients with Alzheimer's disease and young adult controls).

Discussion

In this study we have shown that a clock drawing task can be constructed that is both internally consistent and strongly associated with an executive test measure. We can confirm the impression of Huntzinger *et al*³³ that clock drawing would be useful to clinicians in busy outpatient practices. The CLOX is reliable, easy to administer, and well tolerated by elderly patients. Because many elderly adults are resistant or non-compliant with formal attempts to document their cognitive performance, a clock drawing assessment could improve testing compliance, especially in outpatient, community, and residential settings where professional examiners are not available.

We found that CLOX1 and CLOX2 scores were strongly associated with both the EXIT25 and MMSE. These associations persisted after adjusting for age and education, although education's range was limited by our sample frame.³⁴ Construct validity is suggested by the finding that the EXIT25 accounted for most of the variance in CLOX1 scores, after adjusting for the MMSE, whereas the opposite was found for CLOX2 scores.

Subject performance on CLOX subscales disclosed interesting information about both

well elderly subjects and patients with Alzheimer's disease. Significant fractions of both groups presented below the fifth percentile for young adult controls on one or more CLOX subscales (n =37 (82%) of Alzheimer's disease cases; n =7 (16%) of controls). The pattern of these deficits in Alzheimer's disease suggests a generalised dementing illness. Twenty seven (60%) patients with Alzheimer's disease failed both CLOX subscales. By contrast, no controls presented below this threshold on both subtests.

The cognitive impairments we found in well elderly subjects suggest relatively isolated ECF impairment. Six (14%) elderly controls failed only the CLOX1 subscale, 12 (27%) failed the EXIT25 at 10/50. By contrast, only one elderly control (2.2%) failed the MMSE at 24/30. As Alzheimer's disease affects posterior cortical regions before invading the frontal cortex,³⁵ isolated ECF impairment is not likely to represent early Alzheimer's disease. On the contrary, many non-Alzheimer's disease medical disorders, including subcortical stroke, depression, polypharmacy, and hypothyroidism might be expected to affect ECF more than posterior cortical function.^{18 20} The CLOX may provide a practical means to screen for these "reversible" dementias in community settings.

However, independent of these diseases, there are also reports of (1) isolated age associated decline in ECF testing,^{36 37} (2) disproportionate frontal system atrophy on MRI,³⁸ and (3) disproportionate frontal system hypometabolism by SPECT in healthy elderly controls relative to young adults.³⁹ These studies support the phenomenological overlap between well elderly subjects and those with isolated frontal system dementias.^{40 41} The CLOX may provide a means of detecting this condition. In this study, only age, CLOX1, and EXIT25 scores discriminated between our young and elderly control groups.

The CLOX2 subtest, like traditional cognitive tests, implicitly targets posterior cortical deficits. Recent studies suggest that differences in right parietal metabolism discriminate Alzheimer's disease subgroups with and without constructional impairment.^{32 42 43} CLOX2 scores discriminate Alzheimer's disease subgroups with and without gross constructional impairment, even after adjusting for severity of dementia, whereas the pattern of CLOX1/CLOX2 scores accurately classifies 91.9% of patients with Alzheimer's disease on this basis.

In this regard, our data are consistent with those obtained by Sawada *et al*.⁴⁴ They showed qualitative differences among patients with dementia for the pattern of SPECT perfusion deficits in the right parietal and frontal cortices. As we have noted, the patients with dementia differed from elderly and young adult controls in both indices. All patients with dementia showed frontal cortical hypometabolism relative to controls, but subsets among them differed with in right parietal perfusion. The relation of the CLOX to cortical pathology/perfusion has yet to be determined.

In summary, the CLOX is an internally consistent measure that is easy to administer and

displays good reliability between raters. It is strongly associated with both MMSE and EXIT25 scores. The pattern of clock drawing failures may be useful in the discrimination of clinically homogenous Alzheimer's disease groups, or in the discrimination of Alzheimer's disease from non-Alzheimer's disease cases. These issues remain to be explored in future studies.

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- 44 Sawada H, Udaka F, Kameyama M, et al. SPECT findings in Parkinson's disease associated with dementia. *J Neurol Neurosurg Psychiatry* 1992;55:960-3.

Engagement Rating Form

Subject Code _____ Date _____ Assent _____

1. Level of Participation. Rate the subject's level of participation for 50% or more of the time engaged in the activity session. Select one of the following:

0. Dozing: eyes closed

1. Null: physically inactive, eyes open but not focused on a particular person or event and no purposeful activity apparent

2. Passive: paying attention to the activity or the interventionist or commenting on the activity while not directly engaging in the activity

3. Active: physically or verbally engaging in the steps of the activity

2. Time on Task. Use a stop watch to measure time on task. Once the subject is engaged in an activity, continue timing for 30 minutes or until the subjects disengages. Disengagement is demonstrated by the subject's dozing, negative remarks about the activity, turning away from the interventionist/activity, asking to leave, leaving or attempting to leave the area.

Minutes _____ Seconds _____

Appendix C
Consent Documentation



Implied Informed Consent Form for Family- Group I
The Pennsylvania State University

***Title of Project:* Recreational Stimulation for Elders as A Vehicle to Resolve DSD:
RESERVE-DSD**

Principal Investigator:

Ann M. Kolanowski PhD, RN

Address: 106 Health & Human Development East, University Park, Pa.

Phone: (814) 863-9901; amk20@psu.edu

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DO NOT REMOVE OR MODIFY	
IRB#33443	Doc. #1003
The Pennsylvania State University	
Institutional Review Board	
Office for Research Protections	
Approval Date: 01/28/2013 SJH	
Expiration Date: 01/23/2014 SJH	

Other Principal Investigator:

Donna Fick, PhD, RN

Address: 307 Health & Human Development East, University Park, Pa.

Phone: (814) 865-9325; dmf21@psu.edu

Purpose of the Study: Many older adults who are hospitalized experience periods of confusion that lasts after they are discharged. We do not know what causes this confusion but there are many things that can put people at risk such as dementia, medications, stress, and surgery. Confusion interferes with rehabilitation and may cause mental decline. We are trying to find ways to help older adults who experience confusion to recover more quickly so they regain their health and return to their homes. One of the ways we help older adults who have confusion is to provide them with specially designed mentally stimulating activities. We will be testing these activities in our Penn State research project. You are being asked to participate in this project because you are the responsible party for a patient who will receive these activities in our study.

Procedures to be followed: You will be asked to do several things so we can work with the patient in this study: provide us with information on the patient's past education, leisure activities and work history, provide us with information on the patient's activity interests, provide us with information on the patient's personality, rate how satisfied you were with the activities we provided for the patient, and allow us to call you 3 months after the start of this study so we can ask you questions about the mental status of the patient and where he/she is currently residing.

Discomforts and Risks: There are no risks in participating in this research beyond those experienced in everyday life. Some of the questions are personal and might cause discomfort.

Benefits to you: You may enjoy participating in this study.

Potential benefits to society: The findings from this project may help health care professionals understand more about how to care for older adults who are confused following hospitalization.

Duration/Time: It will take approximately 20 minutes to complete the past education, work and leisure questionnaire, 10 minutes to complete the activity interests, 30 to 40 minutes to complete

the personality information, 2 minutes to complete the satisfaction survey and 10 minutes for the 3-month phone follow up.

Statement of Confidentiality: Your participation in this research is confidential. The surveys do not ask for any information that would identify you. The Pennsylvania State University's Office for Research Protections, the Institutional Review Board and the Office for Human Research Protections in the Department of Health and Human Services may review records related to this research study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared because your name is in no way linked to your responses.

Right to Ask Questions: Please contact Ann Kolanowski at 814-863-9901 or Donna Fick at 814-865-9325 with questions, complaints or concerns about this research. You can also call this number if you feel this study has harmed you. If you have any questions, concerns, problems about your rights as a research participant or would like to offer input, please contact The Pennsylvania State University's Office for Research Protections (ORP) at (814) 865-1775. The ORP cannot answer questions about research procedures. Questions about research procedures can be answered by the research team.

Voluntary Participation: Your decision to be in this research is voluntary. You can stop at any time. You do not have to answer any questions you do not want to answer. Refusal to take part in or withdrawing from this study will involve no penalty or loss of benefits you would receive otherwise.

You must be 18 years of age or older to take part in this research study.

Answering our questions and completing the survey implies that you have read the information in this form and consent to take part in the research. Please keep this form for your records or future reference.



Implied Informed Consent Form for Family- Group II
The Pennsylvania State University

Title of Project: **Recreational Stimulation for Elders as A Vehicle to Resolve DSD: RESERVE-DSD**

Principal Investigator:

Ann M. Kolanowski PhD, RN

Address: 106 Health & Human Development East, University Park, Pa.

Phone: (814) 863-9901; amk20@psu.edu

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Institutional Review Board	
Office for Research Protections	
Approval Date: 01/28/2013 SJH	
Expiration Date: 01/23/2014 SJH	

Other Principal Investigator:

Donna Fick, PhD, RN

Address: 307 Health & Human Development East, University Park, Pa.

Phone: (814) 865-9325; dmf21@psu.edu

Purpose of the Study: Many older adults who are hospitalized experience periods of confusion that lasts after they are discharged. We do not know what causes this confusion but there are many things that can put people at risk such as dementia, medications, stress, and surgery. Confusion interferes with rehabilitation and may cause mental decline. We are trying to find ways to help older adults who experience confusion to recover more quickly so they regain their health and return to their homes. One of the ways we help older adults who have confusion is to provide them with specially designed mentally stimulating activities. We will be testing the effectiveness of this approach in our Penn State research project. You are being asked to participate in this project because you are the responsible party for a patient in this study.

Procedures to be followed: You will be asked to do several things so we can work with the patient in this study: provide us with information on the patient's past education, leisure activities and work history, provide us with information on the patient's personality, and allow us to call you 3 months after the start of this study so we can ask you questions about the mental status of the patient and where he/she currently is residing.

Discomforts and Risks: There are no risks in participating in this research beyond those experienced in everyday life. Some of the questions are personal and might cause discomfort.

Benefits to you: You may enjoy participating in this study.

Potential benefits to society: The findings from this project may help health care professionals understand more about how to care for older adults who are confused following hospitalization.

Duration/Time: It will take approximately 20 minutes to complete the past education, work and leisure questionnaire, 30 to 40 minutes to complete the personality information, and 10 minutes for the 3-month phone follow up.

Statement of Confidentiality: Your participation in this research is confidential. The surveys do not ask for any information that would identify you. The Pennsylvania State University's Office for Research Protections, the Institutional Review Board and the Office for Human Research Protections in the Department of Health and Human Services may review records related to this research study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared because your name is in no way linked to your responses.

Right to Ask Questions: Please contact Ann Kolanowski at 814-863-9901 or Donna Fick at 814-865-9325 with questions, complaints or concerns about this research. You can also call this number if you feel this study has harmed you. If you have any questions, concerns, problems about your rights as a research participant or would like to offer input, please contact The Pennsylvania State University's Office for Research Protections (ORP) at (814) 865-1775. The ORP cannot answer questions about research procedures. Questions about research procedures can be answered by the research team.

Voluntary Participation: Your decision to be in this research is voluntary. You can stop at any time. You do not have to answer any questions you do not want to answer.

You must be 18 years of age or older to take part in this research study.

Giving us the requested information implies that you have read the information in this form and consent to take part in the research. Please keep this form for your records or future reference.

The Pennsylvania State University

Consent for Participants and Responsible Party

**Title of Project: Recreational Stimulation for Elders As A Vehicle to Resolve DSD:
RESERVE-DSD**

Principal Investigator: Ann M. Kolanowski PhD, RN

Address: 106 HHDE, University Park, Pa.

Phone: (814) 863-9901

Other Principal Investigator: Donna Fick, PhD, RN

Address: 307 HHDE, University Park, Pa.

Phone: (814) 865-9325

1. Purpose of the study: Many older adults who are hospitalized experience periods of confusion that lasts after they are discharged. We do not know what causes this confusion but there are many things that can put people at risk such as dementia, medications, stress, and surgery. Confusion interferes with rehabilitation and may cause mental decline. We are trying to find ways to help older adults who experience confusion to recover more quickly so they regain their health and return to their homes. One of the ways we help older adults who have confusion is to provide them with care that reduces risk factors, such as making sure they sleep well, or providing them with their hearing aides and glasses so they see and hear what is going on in the environment. Another way is to provide them with activities that stimulate their minds. We will be testing these approaches in our Penn State research project. You are being asked to participate in this project because you have memory problems and are experiencing some confusion at this time.

2. Procedures to be followed: After you give us written consent, the Project Director (PD) will collect some of your saliva by using a Q-tip like swab. We do this to test for a gene that puts people at risk for dementia. We also ask you questions about your past education, leisure activities and work experience. Then the PD will assign you to one of two groups in a random fashion (like a flip of a coin): usual best practice care or mental activities plus usual best practice care.

If you are in the usual best practice group you will receive care from the nursing home staff and a trained research assistant will visit you each day for up to 30 days or until you are discharged (whichever comes first). This research assistant will ask you questions about your mental status, the degree of confusion you are experiencing, and will rate your pain and how well you can perform self-care activities. We will also review your medical chart on a weekly basis and note the medications and therapies you are receiving, any nursing care you have for confusion, and will note the date you are discharged and the place where you go (home, nursing home) after discharge. Three months after you start the study we will call you to check on your mental status and to see when and where you were discharged (if we don't already know).

If you are assigned to the mental activities plus usual best practice group you will receive everything that the usual best practice group does, but in addition a second trained research assistant will also visit you each day for up to 30 days or until discharge (whichever comes first) during the afternoon hours. They will work with you for 30 minutes doing mentally stimulating activities. These simple, enjoyable activities alert you and may help your short-term memory, concentration and attention. They include games and activities such as “Name that Tune”, “Finish the Phrase”, “Clock Work”, and “Hand Pantomime.” The research assistant will note how long you participated in the activity and your level of participation. At discharge (or after 29 days of activities) we will ask you, your nurse and your responsible party a few simple questions to see if you were satisfied with the activities. We do this so we can improve the way we deliver these activities.

3. Discomforts and risks: The risks to you are no greater than that normally experienced in every day life. The activities we use in this study are similar to those used in nursing homes as part of routine recreational care. You may become bored with the activities or may not be interested in participating in activities when we visit you. If you tell us that you do not like the activity, we will stop the activity. We are attaching a script to this consent form that shows what we will say to you before we begin activities and assessments. Older adults who are in rehabilitation are usually not fully recovered from their hospitalization and need extra care for a period of time. We train all of our research assistants about safety issues, including fall prevention, when working with older adults in rehabilitation settings. If you should injure yourself during an activity, we will notify the nurse in charge immediately so they can contact your primary care provider for any necessary follow-up. The PD on this project has extensive training and experience working with older adults and will stop any procedures that seem to up set you.

4. a. Benefits to me: You may enjoy the visits you receive while participating in this study, and your confusion may resolve more quickly as a result of participation in this study.

b. Potential benefits to society: The findings from this project may help health care professionals understand more about how to care for older adults who are confused following hospitalization.

5. Alternative procedures which could be utilized: There are no non-drug alternatives to the procedures we are using to reduce confusion. Medications are sometimes prescribed for confusion but they may cause undesirable side effects such as excess sleepiness.

6. Time duration of the procedures and study: You will be involved in the project for up to a total of 30 days. We will ask you questions that will take approximately 30 minutes each day. If you are in the mental activity group, the activities will take an additional 30 minutes per day for up to 30 days.

7. Statement of confidentiality: Your participation in this research is confidential. All records associated with your participation in the study will be subject to the usual confidentiality standards applicable to medical records (e.g., such as records maintained by physicians, hospitals etc.), and in the event of any publication resulting from the research no personally identifiable

information will be disclosed. The following may review and copy for monitoring purposes records related to this research: The Office of Human Research Protections in the U.S. Dept. of Health and Human Services; The Pennsylvania State University Institutional Review Board; The Pennsylvania State University Office for Research Protections. All data obtained from this study will be stored in locked file cabinets in the investigator's research office. Only authorized research personnel will have access to these data.

8. Right to ask questions: Please contact Dr. Ann Kolanowski at 814-863-9901 or 570-288-8183 with questions, complaints or concerns about this research. You can also call these numbers if you feel this study has harmed you. If you have any questions, concerns, problems about your rights as a research participant or would like to offer input, please contact The Pennsylvania State University's Office for Research Protections (ORP) at (814) 865-1775. The ORP cannot answer questions about research procedures. Questions about research procedures can be answered by the research team.

9. Compensation: While there is no monetary compensation, there are no costs associated with your participation in this study.

10. Injury Clause: Medical care is available in the event of injury resulting from research but neither financial compensation nor free medical treatment is provided. You are not waiving any rights that you may have against the University for injury resulting from negligence of the University or investigators.

11. Voluntary participation: Your decision to be in this research is voluntary. You can stop at any time. You do not have to answer any questions you do not want to answer. Refusal to take part in or withdrawing from this study will involve no penalty or loss of benefits you would receive otherwise.

12. In the unlikely event that we discover a previously unknown condition during screening or other procedures, we will notify nursing home personnel and you for follow up by your primary care provider.

13. HIPAA: Health information about you will be collected from your medical chart as part of this research study. This information includes:

- Medical diagnoses
- Medical activity order
- Medications currently prescribed
- Therapies currently prescribed
- Nursing care given for confusion
- Discharge disposition

By signing this form you are allowing the people/groups identified in the next paragraph to use this information, but only to use it within this study. You will not be identified by name, social security number, address, phone number or by any other direct personal identifier in research records. You will be assigned a code number and the list that matches your name with the code number will be kept in a locked file cabinet in Dr. Kolanowski's office.

The following people/groups are allowed to use your nursing home resident's health information:

Ann Kolanowski, PhD, RN the Principal investigator
Donna Fick, PhD, RN the Co- Principal investigator
Malaz Boustani, MD, medical consultant
Other members of the research team
The Pennsylvania State University Institutional Review Board and Office for Research Protections
The Office of Human Research Protections in the U.S. Department of Health and Human Services

Once your health information has been disclosed to anyone outside of this study, the information may no longer be protected under this authorization. Your permission for the use and sharing of your health information will continue indefinitely.

The activities we deliver and the procedures we use in this research study cannot be provided unless you allow the use of your health information. It is requested that you sign this form. Your permission for the use of this information will continue indefinitely.

You are free to withdraw your permission for the use and sharing of your health information, but you must do this in writing as indicated in the PSU Privacy Notice. If you do decide to withdraw, we ask that you contact Dr. Ann Kolanowski in writing and let her know that you are withdrawing from the research study. Her mailing address is: 106 Health & Human Development East, Penn State University, University Park, Pa. 16802-3506.

If you withdraw your permission, we will no longer use or share medical information about you for the reasons covered by your written authorization, except when the law allows us to continue using your information. We are unable to take back anything we have already done or shared with your permission, and we are required to keep our records of the care that we provided to you until six years following completion of this study.

This is to certify that you consent to and give permission for your participation as a volunteer in this program of investigation. You will receive a signed copy of this consent form.

I have read this form, and understand the content of this consent form.

Participant/Legally Authorized Representative Date

Participant Date

I, the undersigned, have defined and explained the studies involved to the above volunteer.

Person obtaining the consent Date

VITA

Nikki L. Hill

213 Bellvue Circle, State College, PA 16803, nikki.hill@psu.edu

EDUCATION

- August 2013 **Doctor of Philosophy in Nursing**
Pennsylvania State University, University Park, PA
Dissertation Title: *Personality as a Moderator of Cognitive Stimulation Outcomes in Individuals at High Risk for Cognitive Decline*
Minor: *Gerontology*
- 2009 **Master of Science in Nursing**
Pennsylvania State University, University Park, PA
Clinical Nurse Specialist Program, Adult Health
- 2007 **Bachelor of Science in Nursing**
Pennsylvania State University, University Park, PA
with Highest Distinction and with Honors, Schreyer Honors College
- 2000 **Bachelor of Science in Biology**
Pennsylvania State University, University Park, PA

PREDOCTORAL FUNDING

- Ruth L. Kirschstein National Research Service Award, 2012-2015
Grant #: 1F31NR013304-01
- John A. Hartford Foundation Building Academic Geriatric Nursing Capacity (BAGNC) Predoctoral Scholar, 2009-2011

RESEARCH EXPERIENCE

- 2010 – present **Research Assistant/Graduate Assistant**
Recreational Stimulation for Elders as a Vehicle to resolve DSD, Penn State University
PIs: Ann Kolanowski, PhD & Donna Fick, PhD
Funded by: NINR R01 NR012242
- 2006 – 2007 **Research Assistant**
Delirium in Persons with Dementia, Penn State University; PI: Donna Fick, PhD
Funded by: NIA R03 AG023216-01A1
- 2005 – 2006 **Research Assistant**
A Prescription for Enhancing Resident Quality of Life, Penn State University; PI: Ann Kolanowski, PhD; Funded by: NINR R01 NR008910-01

SELECTED PUBLICATIONS

- Kolanowski, A., Hill, N., Clare, L., & Marx, P. (2012). Practical protocol for implementing cognitive stimulation in persons with delirium superimposed on dementia. *Non-Pharmacological Therapies in Dementia*, 2(2).
- Kolanowski, A., Fick, D., Yevchak, A., Hill, N., Mulhall, P., & McDowell, J. (2012). Pay Attention! The critical importance of assessing attention in older adults with dementia. *Journal of Gerontological Nursing*, 38(11), 23-27.
- Kolanowski, A., Bossen, A., Hill, N., Guzman-Velez, E., & Litaker, M. (2012) Factors associated with sustained attention during an activity intervention in persons with dementia. *Dementia and Geriatric Cognitive Disorders*, 33(4), 233-239.
- Hill, N., & Kolanowski, A. (2011). Plasticity in early Alzheimer's disease: An opportunity for intervention. *Topics in Geriatric Rehabilitation*, 27(4), 257-267.
- Hill, N., Kolanowski, A, Milone-Nuzzo, P., & Yevchak, A. (2011). Culture change models and resident health outcomes in long-term care. *Journal of Nursing Scholarship*, 43(1), 30-40.
- Hill, N., Kolanowski, A., & Kürüm, E. (2010). Agreeableness and activity engagement in nursing home residents with dementia: A pilot study. *Journal of Gerontological Nursing*, 36(9), 45-52.

LICENSURE

Commonwealth of Pennsylvania Department of State
Bureau of Professional and Occupational Affairs
Licensed Registered Nurse #RN585324
Expiration Date: 10/31/2014

SCHOLARSHIPS & AWARDS

- Center for Integrated Healthcare Delivery Systems
Scholarship, 2012-2013
- Pennsylvania Higher Education Foundation Nursing
Education Grant, 2007-2008
- Sigma Theta Tau Beta Sigma Chapter Academic
Achievement Award, 2007
- Chianna and Usharani Reddy Mission Award,
Schreyer Honors College, 2007
- Student Marshall, College of Health & Human
Development, 2007
- Schreyer Honors College Summer Internship Grant
- Nightingale Awards of Pennsylvania Scholarship
Women's Leadership Initiative, Class of 2005-2006
- Leslie Savino Scholarship
- Dean's List, 2003-2007

TEACHING EXPERIENCE

- 2009 **Clinical Instructor**
Penn State University School of
Nursing, University Park, PA
Course: *Health Assessment*
- 2006 – 2008 **Teaching Assistant**
Penn State University School of
Nursing, University Park, PA
Courses: *Nursing Care of the Older Adult, Health Assessment, Nursing Care of the Adult Client (Complex Problems), Pathophysiology, Introduction to Pharmacological Concepts*