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The Relationship between Subsyndromal Symptomatic Depression and Cognitive Dysfunction

Bryce Jacobson

LOMA LINDA UNIVERSITY
School of Behavioral Health
in conjunction with the
Department of Psychology

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Depression and Cognitive Dysfunction

by

Bryce Jacobson

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Each person whose signature appears below certifies that this project in his/her opinion is adequate, in scope and quality, as a project for the degree Doctor of Psychology.

_____, Chairperson
Grace J. Lee, Assistant Professor of Psychology

_____
Colleen A. Brenner, Associate Professor of Psychology

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ABBREVIATIONS

SSD	Subsyndromal Symptomatic Depression
MDD	Major Depressive Disorder
MCI	Mild Cognitive Impairment
AD	Alzheimer's Disease
CSF	Cerebrospinal Fluid
APOE	Apolipoprotein E
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
FDG	Fluoro-2-deoxy-d-glucose
CNS	Central Nervous System
HPA	Hypothalamic-pituitary-adrenal axis
GDS	Geriatric Depression Scale
DSM	Diagnostic and Statistical Manual
MMSE	Mini-Mental State Exam
MOCA	Montreal Cognitive Assessment
RAVLT	Rey Auditory Verbal Learning Test
RCFT	Rey Complex Figure Test
WAIS-IV	Wechsler Adult Intelligence Scale, Fourth Edition
TMT	Trail Making Testing
WMS-IV LM	Wechsler Memory Scale, Fourth Edition, Logical Memory
BNT	Boston Naming Test
COWAT	Controlled Oral Word Association Test

ABSTRACT OF THE DOCTORAL PROJECT

The Relationship between Subsyndromal Symptomatic
Depression and Cognitive Dysfunction

by

Bryce Jacobson

Doctor of Psychology, Graduate Program in Psychology
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Dr. Grace L. Lee, Chairperson

Subsyndromal Symptomatic Depression (SSD), or subthreshold depression,
affects roughly 15% of community-dwelling older adults and puts them at increased risk
for developing Major Depressive Disorder (MDD), which represents a risk factor for
Alzheimer's Disease (AD) and may expedite disease progression. While the relationship
between MDD and AD has been well established, the interaction between SSD and
cognitive functioning has not been explored in depth. Further, clinicians have long
postulated that depression is not a monolithic disorder but rather a group of disorders
which are heterogeneous in onset, symptoms, course, and treatment. One hundred and six
participants, 65 and older were recruited as part of the Adventist Health Study-2
Cognition and Neuroimaging Substudy and underwent comprehensive
neuropsychological testing. Results of an independent samples t-test revealed that
individuals who met criteria for SSD performed significantly worse in the immediate
recall over five learning trials on the Rey Auditory Verbal Learning Test (RAVLT) than
individuals who did not report depressive symptomatology. Further, a hierarchical
regression analysis evidenced that depressive symptoms categorized as "hopelessness",
"dysphoric mood", and "cognitive impairment" were significant predictors of global
cognitive functioning within our SSD sample. These findings suggest that SSD—

specifically when symptoms are related to "hopelessness", "dysphoric mood", and "cognitive impairment"—has a significant impact on cognition. Future research should utilize a longitudinal study design that examines conversion rates of SSD to MCI/dementia to conclude that SSD represents a clinical marker of dementia. If identified as a viable clinical marker, early detection and treatment of SSD could potentially prevent worsening of depression symptoms as well as delay—or even curb— the manifestation of MCI/Dementia in later life.

CHAPTER ONE

INTRODUCTION TO DEMENTIA

Dementia can be defined as a group of symptoms which are characterized by a loss in cognitive functioning which significantly impacts one's day-to-day activities (Schoenberg & Scott, 2011). While there are several different types of dementias which are classified by etiology and presenting symptoms, the most common and colloquially known form is Alzheimer's Disease (AD). AD accounts for roughly 50% of all dementia cases with 35% being the sole result of AD pathology while another 15% is due to mixed pathologies of both AD and Vascular Dementia (Schoenberg & Scott, 2011). The majority of those diagnosed are over the age of 65 and exhibit severe memory and functional impairments. In the United States, nearly 5 million individuals are living with AD and estimates suggest this will increase to 14 million by 2050, highlighting the significance and a pressing need to increase our understanding of its cause and course (Hebert, Weuve, Scherr, & Evans, 2013). While AD is not fully understood, it is believed that the course of the disease begins with a prodromal period that begins approximately 20 years before any noticeable cognitive deficits emerge (Shaw et al., 2009). However, by the time these deficits manifest, the neurodegeneration is often considered too severe to respond to current therapies. Therefore, efforts have been made to understand and identify the underlying pathology as well as other risk factors before extensive neurodegeneration has taken place in the hopes of early intervention. To understand AD, many researchers have examined Mild Cognitive Impairment (MCI), which can be defined as an intermediary state between normal aging and AD (Schoenberg & Scott, 2011). Specifically, researchers have examined potential biological markers which may

predict conversion from MCI to AD.

Efforts to Detect the Prodromal Stages of Alzheimer's Disease

Mild Cognitive Impairment

Mild Cognitive Impairment (MCI) describes individuals who are in an intermediate state between normal aging and dementia (Schoenberg & Scott, 2011). Typically, the MCI patient will exhibit deficits in at least one cognitive domain (1.5 or more standard deviations below the age-adjusted mean) and may present with memory complaints but exhibit no significant impairments in their daily functioning (Petersen et al., 2001). Within MCI, there are several different subtypes which can be categorized as amnestic or nonamnestic as well as single-domain or multiple domain impairments. Amnestic MCI involves impairments in the domain of memory while non-amnestic MCI involves impairments in other non-memory domains. Single-domain indicates that the individual is only experiencing significant impairments in one cognitive domain while multiple domain is indicative of multiple domain impairments (Petersen et al., 2001). It has been theorized that specific MCI subtypes may predict the type of dementia that the patient converts to. For example, amnestic MCI patients might be more likely to progress to AD while a non-amnestic MCI patient exhibiting executive deficits might be more inclined to develop Frontotemporal Dementia (Schoenberg & Scott, 2011). However, the current research indicates that these patterns of progression aren't as clear cut (Kondo et al., 2016; Luis et al., 2004; Manly et al., 2008). Aside from differential patterns of cognitive deficits, past research has indicated that specific neuropsychiatric symptoms

may be more representative of different types of dementia. For instance, delusions may be more characteristic of AD, while depression is more common in vascular dementia, and hallucinations are more prevalent in dementia with Lewy bodies (Chiu, Tsai, Chen, Chen, & Lai, 2016; Lyketsos et al., 2000). Therefore, examining neurocognitive profiles in conjunction with neuropsychiatric symptoms may have greater predictive value when categorizing dementia than by MCI subtype alone.

Structural Imaging

The medial temporal lobe, specifically the hippocampus, plays an important role in the consolidation of memory. It is also the location of the earliest neurofibrillary pathology associated with AD (Schoenberg & Scott, 2011). With this in mind, Jack et al. (1999) conducted a longitudinal study examining hippocampal volume in MCI patients as a possible predictor of conversion to AD. Specifically, they wanted to determine whether or not Magnetic Resonance Imaging (MRI) techniques could be used to predict conversion to AD in MCI patients above and beyond the effects of age, apolipoprotein E (APOE) genetic risk factors, hypertension, cognitive performance, and heart disease. Results indicated that smaller hippocampal volume at baseline predicted an increased likelihood of converting to AD from MCI at a 3-year follow up, lending support to the predictive power of structural imaging techniques when detecting early stages of AD.

Functional Imaging

With MRI and other structural imaging techniques established as useful measures in identifying AD biological markers, Mosconi et al. (2004) investigated whether

functional imaging techniques could be used to predict conversion from MCI to AD. Specifically, they wanted to examine whether fluoro-2-deoxy-d-glucose (FDG) Positron Emission Tomography (PET) measures with the Apolipoprotein E (APOE) genotype would be useful in determining whether an MCI patient was at an increased risk of converting to AD. The APOE E4 allele is believed to be the most common susceptibility gene for AD while APOE E2 is believed to have protective qualities against AD (Corder & Caskey, 2009). Those who converted to AD from MCI had lower metabolic activity in the parietal regions of the brain, specifically in the Inferior Parietal Lobule, establishing that functional imaging techniques could be useful predictors of AD conversion. Further, an interaction between APOE E4 and glucose metabolism appeared to indicate that MCI patients who were carriers of the APOE E4 allele presented with even greater reductions in metabolic activity.

Cerebrospinal Fluid

The hallmark pathological features of AD are neurofibrillary tangles and amyloid beta (AB) plaque buildups which typically begin in the hippocampus. Specifically, these buildups are the result of AB peptides 1 – 42, which are the least soluble of the known AB peptides (Schoenberg & Scott, 2011). In an attempt to establish a cerebrospinal fluid (CSF) marker of AD, Shaw et al. (2009) compared AB1-42 CSF levels in a sample of MCI, non MCI, and AD autopsy confirmed patients. Results of their study concluded that CSF AB1-42 was a reliable biomarker in predicting AD with an overall test accuracy of 87%, lending further support to early identification of AD.

Neuropsychological Testing

While biological markers are useful for identifying prodromal stages of AD/Dementia, the most reliable predictor of conversion from MCI to AD is comprehensive neuropsychological testing. Using a longitudinal design, Tabert et al. (2006) evaluated conversion rates of MCI to AD to identify specific patterns of deficits that predict conversion. A comprehensive battery including measures of learning and memory, orientation, abstract reasoning, language, attention, and visuospatial ability was compiled. After three years, 26% of the sample converted to AD from MCI and 50% of those who converted qualified as MCI multiple-domain amnestic patients. When examining specific patterns in the neuropsychological profiles, percent savings from immediate to delayed recall on a test of verbal learning and memory (Selective Reminding Test, SRT) was the strongest predictor of conversion. On the SRT, percent savings describes the number of words recalled after the delay as a proportion of the words recalled before the delay. In addition, an indirect measure of executive function (WAIS-R digit symbol coding), semantic verbal fluency (Animals), and confrontation naming (Boston Naming Test) also predicted conversion. However, after all predictors were added into a single model, only measures of verbal learning and memory and executive function remained statistically significant. These findings, specifically the deficits in executive function and verbal learning and memory, corroborate previous research which has found similar patterns of deficits in the AD patient (Albert, Moss, Tanzi, & Jones, 2001). While deficits in verbal fluency and confrontation naming are often seen in AD patients, these specific patterns of deficits become more apparent as the disease progresses, which might explain why they were not statistically significant

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deficits in this sample of early converts (Schoenberg & Scott, 2011). Regarding the limitations of this study, a measure specifically designed to assess executive function was not utilized. Therefore, future research examining neuropsychological profiles of MCI to AD converts should include specific tests to assess this domain.

Risk Factors

While biological markers such as hippocampal neurodegeneration, inferior parietal lobule metabolism, and AB1-42 CSF levels and clinical markers such as executive and memory deficits are useful in identifying early stages of AD, there is no "gold standard" for early identification. In reality, a combination of these markers is most likely the best predictor of MCI to AD conversion. However, there are some who argue that MCI is in fact an early stage of AD/Dementia (Morris & Cummings, 2005). Therefore, while identification of biological/clinical markers that predict conversion are useful and offer greater insight into the cause of AD, examination of the risk factors/prodromal stages before the onset of MCI might prove more useful in terms of prevention/intervention. Currently, several risk factors of AD have been identified, including: age, female gender, lower levels of education, history of head injury, APOE4, and a history of neuropsychiatric illness (Schoenberg & Scott, 2011; Van der Mussele et al., 2013). Most research on neuropsychiatric illness and dementia has examined depression. This is due to the frequency that major depressive disorder (MDD) co-occurs with dementia. Currently, it is estimated that 20% of all dementia cases have a comorbid diagnosis of MDD (Lyketsos et al., 2002).

CHAPTER TWO

DEPRESSION AND DEMENTIA

While the connection between major depressive disorder (MDD) and AD is undisputed, the exact nature of the relationship remains unclear. While there is some evidence that suggests that MDD is an independent risk factor for AD, other research seems to indicate that it is a prodromal symptom of the disease (Barnes et al., 2012; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). Currently, the consensus on the matter is that MDD in younger adulthood represents an independent risk factor, while depression that first occurs later in life may be a prodromal symptom of AD. MDD, which is often characterized by a depressed mood and loss of interest in activities, is recognized as the leading cause of life-time disability and is estimated to have a 3-month prevalence rate of 7% in the general population and 3-5% in the elderly population (Anstey, von Sanden, Sargent-Cox, & Luszcz, 2007; Chisholm, Sanderson, Ayuso-Mateos, & Saxena, 2004; *Diagnostic and statistical manual of mental disorders: DSM-5™., 5th ed*, 2013). Further, studies examining the conversion rates of Mild Cognitive Impairment to AD found that depressed individuals had a 50% chance of developing AD compared to the 36% conversion rate in the non-depressed group (Lee et al., 2012). This relationship was particularly salient in individuals who exhibited deficits in multiple cognitive domains (Gabryelewicz et al., 2007; Tabert et al., 2006).

Neuropsychiatric Symptoms

While a history of neuropsychiatric illness is associated with an increased risk for developing dementia (Schoenberg & Scott, 2011), Teng, Lu, and Cummings (2007)

conducted a study to further delineate specific neuropsychiatric symptoms that were associated with an increased risk for converting from MCI to AD. To assess for neuropsychiatric symptoms, the Neuropsychiatric Inventory (NPI) was utilized. The NPI is a measure of psychopathology specifically designed to assess for common disturbances in dementia patients, including: Delusions, Hallucinations, Dysphoria, Anxiety, Agitation, Euphoria, Apathy, Irritability, Disinhibition, and Aberrant Motor Activity (Cummings et al., 1994). After a two-year follow up, 23% of the sample converted from MCI to AD, 100% of which endorsed neuropsychiatric symptoms at baseline. Further, symptoms consistent with Depression and Apathy, which can be considered a symptom of MDD (*Diagnostic and statistical manual of mental disorders: DSM-5™., 5th ed*, 2013), were the strongest predictors of conversion.

These findings are consistent with previous longitudinal research examining the conversion rates from MCI to AD in depressed populations. In a study conducted by Modrego and Ferrández (2004), depressed MCI patients were not only more likely to progress to AD but they did so at a much quicker rate. Further, it appeared that the depressed MCI patients who converted early on were those who responded poorly to antidepressants at baseline while those who did respond exhibited a slower progression. This appears to suggest that antidepressants may have a protective effect against the deterioration associated with dementia. In another study examining the conversion rates of MCI to AD in a depressed sample, MCI subtype was also examined as a possible predictor. After a 3-year follow up, results indicated that depressed MCI patients converted at a much higher rate, especially MCI patients who exhibited deficits in multiple domains of cognitive functioning (Gabryelewicz et al., 2007). These findings are

consistent with previous research which has divided MCI patients into different

subgroups (Tabert et al., 2006).

However, not all researchers have been able to replicate these findings. When

Rozzini, Chilovi, Trabucchi, and Padovani (2005) examined MCI to AD conversion rates

in a sample of depressed and non-depressed MCI patients, they did not find any

significant differences. In fact, a greater proportion of those in the non-depressed MCI

sample converted to AD than in the depressed sample. However, the depressed MCI

sample were also being treated for their depression with a selective-serotonin reuptake

inhibitor, which recent research has suggested might have some protective effects against

hippocampal neurodegeneration (Dranovsky & Hen, 2006). Therefore, the lack of

significant differences in conversion may be due to the neuroprotective effects of the

antidepressants the depressed sample were taking. While the aforementioned study does

not support the relationship between depression and dementia, it does offer a glimpse at

possible therapeutic interventions.

Underlying Mechanisms Connecting MDD to AD

As for what biological mechanisms may account for the relationship between

MDD and AD, there is some evidence to suggest some underlying Central Nervous

System (CNS) pathology, specifically in regions associated with monoamine production

such as the locus coeruleus, dorsal raphe nucleus, and substantia nigra (Björklund &

Dunnett, 2007; Michelsen, Prickaerts, & Steinbusch, 2008; Wang, Wang, Wu, Huang, &

Li, 2017). Dysregulation of the monoamines—which includes dopamine, norepinephrine,

and serotonin—is frequently implicated in the development of depression (Dean &

Keshavan, 2017). Zweig et al. (1988) examined neuronal loss and neurofibrillary tangles in AD patients and found that AD patients had greater neuronal loss in the locus coeruleus and the dorsal raphe nucleus than in the control group. Further, this relationship was even more pronounced in AD patients with a comorbid diagnosis of MDD. Other studies examining neuronal loss in the locus coeruelus, substantia nigra, and basal ganglia were able to corroborate these findings by determining that AD patients with MDD had significantly greater neuronal loss in the locus coeruelus as well as the substantia nigra (Förstl, Levy, Burns, Luthert, & Cairns, 1994; Zubenko & Moossy, 1988). These findings suggest that MDD and AD may have similar underlying pathology which may account for why the two often co-occur.

There has been research to suggest that excess glucocorticoids, or stress hormones, may contribute to the connection between MDD and AD. Disturbances in the hypothalamic-pituitary-adrenal axis (HPA), which moderates glucocorticoid activity, have been implicated in having a role in MDD (Cowen, 2010). Further, Cushing's disease, which is characterized by excess cortisol levels, is associated with decreases in hippocampal volume (Starkman, Gebarski, Berent, & Schteingart, 1992). Longitudinal designs examining cortisol levels in patients already diagnosed with AD found that higher levels of cortisol predict more rapid cognitive decline (Huang et al., 2009). Considering that the hippocampus plays a central role in memory and learning and marks the location of early AD pathology, it is possible that excess cortisol levels caused by MDD may play a role in the connection to AD. However, researchers have also found that MDD patients without AD pathology who display excess cortisol levels exhibit cognitive impairments (Hinkelmann et al., 2009). Therefore, whether excess cortisol

levels in MDD represents a risk factor for AD or simply a comorbid diagnosis has yet to be delineated.

Exacerbation of Disability with Comorbid Diagnoses of MDD and AD

The neurodegeneration associated with Alzheimer's Disease not only leads to significant deficits in memory but also in functional ability. As the disease progresses, the AD patient begins to lose their ability to complete instrumental activities of daily living, such as driving, cooking, or assembling tax records. In later stages, they eventually lose their ability to complete more basic activities, such as eating, dressing, and toileting (Schoenberg & Scott, 2011). Further, Major depressive disorder is currently recognized as the leading cause of lifetime disability in the United States (Chisholm et al., 2004). Starkstein, Jorge, Mizrahi, and Robinson (2005) examined the functional and psychopathological impact major and minor depression has in patients with AD. They found that the presence of minor depression was more frequent at latter stages of AD than at earlier stages and that 91% of depressed AD patients reported symptoms of "depressed mood". On measures of self-care, sphincter control, mobility, locomotion, communication, social cognition, and social support, patients with comorbid diagnoses of AD and depression scored significantly worse than non-depressed AD patients. Neuropsychological evaluations found that both major and minor depressed AD patients performed significantly worse on a test of visual construction (WAIS-IV Block Design) than non-depressed AD patients, however, no significant differences were seen on tests of object naming (Boston Naming Test), semantic and verbal fluency (COWAT), verbal memory (Buschke Selective Reminding Test), and attention/working memory (WAIS-IV

Digit Span). AD patients with MDD also exhibited more severe anxiety, apathy, delusions, and parkinsonian symptoms than AD patients with minor depression, suggesting that impairments in AD increase as the severity of depression increases.

While the exact relationship between MDD and AD has yet to be delineated, the connection between the two is undeniable. Not only has MDD been identified as a risk factor/prodromal stage of AD, depression appears to expedite AD decline and exacerbate the functional disability associated with AD. Examination of CNS pathology and the shared underlying mechanisms may partially explain this connection. Considering the modest prevalence rates of MDD and its connection to AD, research examining the treatment of depression in relation to dementia may have some positive implications for the treatment/prevention of AD. However, in the interest of prevention, examination of the intermediary or prodromal stages of MDD and AD/MCI will most likely have more of an impact on intervention and treatment development than an exploration of the latter stages of the disease.

CHAPTER THREE

HETEROGENEITY OF MAJOR DEPRESSIVE DISORDER

Over the past few decades, Major depressive disorder (MDD) has emerged as one
of the most prominent mental health disorders and critical public health concern.
Currently, MDD is the leading cause of life-time disability and the fourth leading
contributor to the global burden of disability worldwide (Chisholm et al., 2004).
However, our understanding of depression, its etiology, and classification is muddled and
there's still much confusion as to what depression is. Depression is a wide-reaching
syndrome that is associated with many different mental health, physical health, and
neurological disorders and not all manifestations of MDD respond to treatment the same,
suggesting the possibility of differing etiologies. Further, depression ranges in severity
and symptom presentation from psychotic to neurotic symptoms (Cole, McGuffin, &
Farmer, 2008). *The Diagnostic and Statistical Manual of Mental Disorders, 5th ed* (2013)
lists nine different symptoms of Major Depressive Disorder while only five need to be
reported for a diagnosis of MDD. Considering these practices, two different people can
be diagnosed with MDD and share only a single symptom. Further, there are vastly
different pathways which a person can reach a depressed state (i.e. loss of a loved one,
fired from job, genetic predisposition) as well as different trajectories of the disorder.

Recovery Patterns

Considering the heterogeneity and vast presentation of MDD, previous
researchers have attempted to delineate specific MDD trajectory patterns. Hybels, Pieper,
Blazer, and Steffens (2016) were able to identify four distinct patterns of recovery in

older adults diagnosed with MDD: a quick recovery class, a persistent moderate symptom class, a persistent high class, and a slow recovery class. It appeared that patients who were categorized as "quick recovery" had retained more of their instrumental activities of daily living (i.e. driving, cooking) and had higher levels of social support while patients who were classified as "persistent high symptom" had the highest levels of perceived stress and the least amount of social support. Further, patients who were classified as "slow recovery" had the earliest age of symptom onset. Results of this particular study imply that different recovery patterns and identifiable external and internal influences (i.e. social support, stress management) might offer insight into different subtypes of MDD.

Subscales by Symptoms

Other researchers have attempted to identify different subtypes of depression by performing factor analyses on depression indices. The Geriatric Depression Scale (GDS) is a commonly used measure of depression symptoms in older adults. Major strengths of the GDS include its high internal consistency (Cronbach's alpha = .94) and simple "yes" and "no" format. In an attempt to identify possible subcategories of depression, Adams, Matto, and Sanders (2004) performed a confirmatory factor analysis of the 30-item GDS. They were able to identify five distinct subscales: Dysphoric Mood (Cronbach's alpha = .80), Withdrawal-Apathy-Vigor (Cronbach's alpha = .72), Hopelessness (Cronbach's alpha = .65), Cognitive Impairment (Cronbach's alpha = .52), and Anxiety (Cronbach's alpha = .59). The Dysphoric Mood subscale describes depressed mood, sadness, emptiness, and an overall lack of satisfaction with life, which can be interpreted as the

"core" of a depression. The Hopelessness subscale encompassed symptoms of hopelessness, helplessness, and worthlessness, which the authors posit might be particularly useful when screening for suicidal ideation. The Withdrawal-Apathy-Vigor subscale incorporates items related to interests and activities and may represent behaviors and experiences that are influenced by age. The Anxiety subscale described obsessive ruminating, or worry, which captures the thinking and emotion problems that are common in MDD. Lastly, the Cognitive Impairment subscale address symptoms of confusion, concentration, and decision making. While these symptoms are common in MDD patients, they may also be indicative of other conditions such as dementia or a stroke. Implications of this study include the possibility of distinct subcategories of MDD and may improve the utility of the GDS for assessment and treatment purposes.

Subscales and Cognitive Performance

Prior research on depression subscales and cognitive performance has been relatively sparse. However, Turner, Capuano, Wilson, and Barnes (2015) identified the "Negative Affect" subscale on the 15-item GDS to be associated with a faster rate of decline in global cognition. This nine-item subscale makes up the bulk of the 15-item measure and, interestingly, encompasses items from several different subscales identified by Adams et al. (2004) on the 30-item GDS. It includes one item from the Cognitive Impairment subscale ("More problems with memory"), two items from the Dysphoric Mood subscale ("Often get bored", "Most people are better off"), three items from the Withdrawal subscale ("Dropped activities", "Prefer to stay home", "Full of energy"), and three items from the Hopelessness subscale ("Feel helpless", "Feel worthless", "Situation

is hopeless"). Research with the Center for Epidemiological Studies-Depression (CES-D) measure—a 20-item measure of depression—identified the Depressed Affect subscale to associated with poorer performance on a task of non-verbal and abstract reasoning (Brailean et al., 2016). While the CES-D does not share the same wording as the GDS and GDS-15, several items within the Depressed Affect subscale are analogous to the Dysphoric Mood subscale on the GDS.

Subsyndromal Symptomatic Depression

Subsyndromal Symptomatic Depression (SSD), or subthreshold depression, can be defined as the presence of depressive symptoms which do not meet criteria for a diagnosis of depression as described in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (Lyness, Chapman, McGriff, Drayer, & Duberstein, 2009). When assessed with a depression screener such as the Geriatric Depression Scale (GDS), SSD is typically defined as a score that is greater than zero and less than the clinical cutoff (Mackin et al., 2013; Royall, Palmer, Chiodo, & Polk, 2012). It is believed that roughly 15% of community-dwelling older adults and 50% of MCI patients qualify for SSD (Geda et al., 2008; Goldney, Fisher, Dal Grande, & Taylor, 2004). Research has indicated that SSD symptoms in community-dwelling adults may contribute to disability and functional impairments as well as put them at greater risk for developing MDD or dysthymia. (Chopra et al., 2005; Lyness et al., 2007). Further, due to the higher prevalence rates of SSD compared to MDD in the older adult population, SSD cumulatively accounts for greater functional morbidity than MDD (Lavretsky & Kumar, 2002; Lyness et al., 2007). Unfortunately, due to the categorical nature of the *Diagnostic*

and Statistical Manual, those who do not meet the cutoff for a diagnosis of depression are often overlooked. While the relationship between MDD and MCI/Dementia has been well-established, the effects of SSD in community-dwelling older adults on cognitive performance—to our knowledge—has been less extensively examined and results have been mixed. In a study conducted by Mackin, Insel, Aisen, Geda, and Weiner (2012), a baseline diagnosis of SSD in MCI patients was not found to differentiate between AD converters and non-converters. Rather, it appeared that the stability and/or worsening of SSD symptoms over time was a better predictor of conversion. There is suggestion that symptoms of SSD are likely to persist as well as worsen, with SSD patients exhibiting a 7-fold increased risk of developing MDD over the course of a year (Lyness et al., 2009). Further, other researchers have found significant differences in cognitive functioning between SSD individuals and non-depressed individuals in both cross-sectional and longitudinal design studies. For instance, SSD patients perform significantly worse than controls on tests of memory, language, and executive function at baseline (Dillon et al., 2011; Gonzales et al., 2017). Overtime, subclinical mean GDS scores—which is congruent with the current definition of SSD—were found to predict cognitive decline over a three-year period in the domains of attention and executive functioning (Royall et al., 2012). There is also evidence to suggest that specific items on the GDS (memory problems, dropped activities and interests, preference for staying at home, and feelings of helplessness) may be especially relevant in predicting conversion to MCI/AD in SSD patients (Mackin et al., 2012). In a study that utilized autopsy and cognitive assessment data between 1991 and 2001 from the Honolulu-Asia Aging Study (HAAS), researchers found that SSD was significantly associated with subsequent cognitive decline, above and

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beyond the effect of amyloid-related neuropathologies, neurofibrillary tangles, lewy bodies, and ischemic lesions (Royall & Palmer, 2013). Not only does it appear that SSD may be related to cognitive functioning, there is also evidence that indicates it compounds functional disability, which is a diagnostic symptom of dementia. In a 2-year longitudinal study, researchers found that within a sample of MCI participants, those who met criteria for SSD were 1.77 times more likely to have worse Functional Activity Questionnaire (FAQ) scores than those who did not meet criteria, suggesting that SSD exacerbates functional disability in individuals with MCI (Mackin et al., 2013), which corroborates previous findings (Porta-Etessam, Tobaruela-González, & Rabes-Berendes, 2011).When examining neurometabolic differences, cognitively normal SSD patients exhibited decreased fluorodesoxyglucose (FDG) metabolism in mood-related brain regions, which may contribute to an increased risk for MCI/AD conversion (Brendel et al., 2016). SSD patients have also exhibited impaired functional deactivation in the posterior medial cortex (PMC) while similar impairments have been observed in AD patients (Woo, Prince, Petrella, Hellegers, & Doraiswamy, 2009).

While there does appear to be evidence for a link between SSD and MCI/AD, the current literature is limited and a definitive agreement has yet to be reached. However, considering that SSD is associated with cognitive decline and MDD—which is considered a prodromal stage of dementia in late life—it is reasonable to assume that SSD in healthy older adults, particular those who have no prior history of depression, may mark the beginning stages of dementia (Barnes et al., 2012). If further evidence of significant differences in cognitive performance and disability are found in community-dwelling older adults who exhibit SSD compared to those who do not, the implications

could be particularly salient for the treatment and course of MCI/Dementia. For instance, SSD is a treatable condition (Tadić et al., 2010). Studies examining the effectiveness of selective-serotonin reuptake inhibitors, problem-solving therapy, and exercise therapy for the treatment of minor depression showed promising results (Brenes et al., 2007; Oxman, Hegel, Hull, & Dietrich, 2008). Further, a study examining the effectiveness of problem-solving therapy (PST) when treating individuals who presented with both Major Depression and MCI found that PST significantly reduced the burden of disability (Alexopoulos et al., 2011). If individuals who exhibit SSD are exposed to these early intervention techniques, it could potentially delay or even prevent the onset of MCI/Dementia in later life.

CHAPTER FOUR

THE PROPOSED STUDY

Among those with measurable cognitive deficits, cognitive functioning can be perceived as a continuum, broadly encompassing age-associated memory impairment, mild cognitive impairment, and dementia. While it is not unusual to see slight decrements in certain cognitive processes with age, the risk for dementia increases overtime with prevalence rates of 15-20% after age 74 and 30-50% after age 85 (Schoenberg & Scott, 2011). In its broadest definition, dementia is a clinical syndrome characterized by severe impairments in one or more cognitive domains with accompanying functional impairments. There are several different types of dementias which are classified by etiology and presenting symptoms, the most common of which is Alzheimer's Disease (AD).

Neuropsychological testing is useful for identifying those most at risk for cognitive impairment (Jack et al., 1999; Mosconi et al., 2004; Shaw et al., 2009; Tabert et al., 2006). Further, several other risk factors for cognitive impairment have been identified, including: age, family history, certain genetic factors, poor cardiovascular health, previous traumatic brain injuries, and a history of neuropsychiatric illness (Schoenberg & Scott, 2011). Major depressive disorder (MDD), specifically, has been pinpointed as a particularly salient neuropsychiatric risk factor. Examination of the biological relationship between MDD and dementia—specifically AD—has found shared underlying pathology in the CNS and similar disturbances in the hypothalamic-pituitary-adrenal axis (Huang et al., 2009; Zweig et al., 1988). The current consensus is that MDD represents an independent risk factor for AD early in life while late-life MDD can be

construed as a prodromal stage of the disease (Barnes et al., 2012). Symptoms of depression also appear to expedite dementia decline and exacerbate functional disability (Modrego & Ferrández, 2004; Starkstein et al., 2005).

While the relationship between MDD and cognitive impairment has been well-established, less research has examined the effects of minor depression, or subsyndromal symptomatic depression (SSD), on cognitive ability in otherwise healthy, community-dwelling older adults. The current proposed study intends to examine the relationship between SSD and cognitive ability in a sample of healthy, non-demented older adults. If a relationship between SSD and cognitive dysfunction is established, future research can examine SSD's effect on conversion rates to MCI/dementia as well as the efficacy of SSD treatment as preventative care. Implications include the identification of a possible early clinical marker for AD as a point of intervention. Further, MDD is a heterogeneous disorder with differing catalysts, symptoms, trajectories, and outcomes (*Diagnostic and statistical manual of mental disorders: DSM-5™., 5th ed*, 2013; Hybels et al., 2016). To our knowledge, the research is limited on whether specific clusters of depression symptoms are associated with an increased risk for developing MCI/dementia and has not been explored with the 30-item GDS. The proposed study will also attempt to delineate whether specific clusters of depression symptoms are disproportionally associated with cognitive impairment. If a pattern is identified, treatments specifically designed to target symptom clusters can be implemented to streamline the treatment process.

Specific Aims

Aim 1. Determine whether Subsyndromal Symptomatic Depression

is Related to Cognitive Deficits.

Hypothesis: We predict that Subsyndromal Symptomatic Depression (SSD) will

predict cognitive functioning, such that participants who exhibit symptoms of SSD will

perform worse on measures of neuropsychological functioning than participants who do

not exhibit SSD.

Null Hypothesis: There will be no significant differences on measures of

neuropsychological functioning between participants who exhibit SSD and those who do

not.

Aim 2. Determine Whether Specific Symptoms of Depression

are Specifically Tied to Cognitive Deficits.

Hypothesis: We predict that certain clusters of depression symptoms will be

disproportionally associated with deficits in cognitive functioning.

Null Hypothesis: There will be no significant pattern of depression symptoms

associated with deficits in cognitive functioning.

Experimental Plan/Study Design

Subjects

One hundred and six participants, 65 and older were recruited as part of the

Adventist Health Study-2 Cognition and Neuroimaging Substudy (AHS-2 CAN; accessible population). Recruitment began in June 2016 and continued through August 2018. The study was designed to examine relationships between cognitive function and dietary patterns among Seventh-Day Adventist church members over the age of 65. They were informed of the purpose of the study. Exclusion criteria included a diagnosis of dementia, a history of significant neurologic disease or insult, substance abuse or dependence within the last 2 years, a medical illness that could affect cognition, and a GDS score greater than 9. Results of the study will, ideally, be generalizable to healthy, older Americans with non-clinical depression (theoretical population).

Methods

After providing informed consent, participants underwent a 2-hour comprehensive neuropsychological battery in Loma Linda University's Neuropsychological Assessment and Neuroimaging Lab. The battery measured multiple domains of functioning, including: Premorbid Verbal Intelligence, Attention/Processing Speed, Language, Visuospatial ability, Verbal Memory, Non-verbal Memory, and Executive Functioning. Presence of depressive symptoms was assessed using the Geriatric Depression Scale (GDS). Participants' background and demographic information was also collected, including: age, gender, marital status, ethnicity, handedness, years of education, vision and hearing deficits, psychiatric history, medication use, social history, and family history of neurological/psychiatric problems. The battery was administered by a trained lab assistant using a standardized procedure. Total time to complete an assessment took approximately 2 hours. The full

neuropsychological battery can be found in Appendix B. All key personnel have completed training required to work with human subjects (see Appendix C).

Materials

Mini-Mental State Exam (MMSE)

The Mini-Mental State Exam is a 30-point screening tool used to measure global cognitive functioning and is most commonly used to screen for dementia. Administration takes 5 to 10 minutes and examines orientation, registration, attention and calculation, recall, language, and visual construction (Folstein, Folstein, & McHugh, 1975).

Montreal Cognitive Assessment (MOCA)

The Montreal Cognitive Assessment is a 30-point screening measure used to assess for mild cognitive impairment. Administration takes 5 to 10 minutes and examines visuospatial/executive ability, naming, memory, attention, language, abstraction, delayed recall, and orientation (Nasreddine et al., 2005).

Rey Auditory Verbal Learning Test (RAVLT)

The Rey Auditory Verbal Learning Test is a measure of short-term auditory-verbal memory, rate of learning, learning strategies, retroactive and proactive interference, retention, confabulation, and retrieval. Initial administration takes 15 minutes. A delayed trial is administered 30 minutes after initial administration (A. Rey, 1958).

Rey Complex Figure Test (RCFT)

       The Rey Complex Figure Test is a measure of visuospatial abilities, visual memory, and planning. The participant is asked to reproduce a complex figure, first by copying and later from memory following a three minute delay (André Rey & Osterrieth, 1941)

Wechsler Adult Intelligence Scale-IV Coding (CD)

       Coding is subtest of the WAIS-IV and measures psychomotor and processing speed. The participant is required to scan and pair digits with their assigned symbols (Wechsler, 2008).

Stroop Test

       Stroop Word Trials and Color Trials are measures of verbal information processing speed while Color/Word Trials is an executive measure of response inhibition (Golden, Freshwater, & Golden, 2002).

Wechsler Adult Intelligence Scale-IV Digit Span (DS)

       Digit Span is a subtest of the WAIS-IV and measures working memory, attention, encoding, and auditory processing. The participant is required to recall a series of numbers in order (Wechsler, 2008).

Trail Making Test Parts A & B (TMT A&B)

       Trails A measures processing speed, psychomotor speed, and visual motor

tracking while Trails B measures set-shifting and cognitive flexibility, which are executive skills. Trails A consists of 25 circles numbered 1-25 distributed over a sheet a paper which the participant must connect in consecutive order. Trails B consists of 25 circles—numbers and letters—which the participant must alternate between in consecutive order (Reitan & Wolfson, 1986).

Wechsler Memory Scale-IV Logical Memory (LM)

Logical Memory (LM) is a subtest of the WMS-IV. The participant is presented with two short stories which they must recall immediately (LMI) and then after a 30-minute delay (LMII). This subtest measures immediate, delayed, and recognition memory of contextualized verbal information ("Wechsler Memory Scale--Fourth Edition," 2009).

Boston Naming Test (BNT)

The Boston Naming Test is a 60-item measure of confrontational object naming. The participant is presented with a series of images which they must name (Kaplan, Goodglass, & Weintraub, 2001).

Controlled Oral Word Association Test (COWAT)

The Controlled Oral Word Association Test is a verbal fluency test that measures spontaneous production of words either beginning with a designated letter (FAS) or belonging to a category (Animals). FAS, specifically, measures phonemic verbal fluency while Animals measures semantic verbal fluency (Ross et al., 2007).

Geriatric Depression Scale Long Form (GDS)

The Geriatric Depression Scale is a 30-item questionnaire used to identify depression in the elderly. Items reflect depressive symptoms and are answered in a "yes" or "no" format (Yesavage et al., 1983).

Clinical History Form

The Clinical History Form is used to obtain demographic and other background information from the participant. Information collected includes: age, gender, marital status, ethnicity, handedness, years of education, vision and hearing deficits, psychiatric history, medication use, and family history of neurological/psychiatric problems

Operational Definitions

I. Independent Variables

    a. Depression Severity

        i. Non-depressed (GDS = 0)

        ii. Subsyndromal Symptomatic Depression (GDS = 1-9)

    b. Depression Subscales

        i. Dysphoric Mood (GDS items 16, 9, 3, 1, 23, 7, 4, 25, 15)

        ii. Withdrawal-Apathy-Vigor (GDS items 12, 28, 2, 19, 20, 21)

        iii. Anxiety (GDS items 8, 13, 6, 18)

        iv. Cognitive (GDS items 26, 30, 29)

        v. Hopelessness (GDS items 22, 10, 17, 5)

II. Dependent Variables

a. Individual Neuropsychological Tests

      i. MMSE

      ii. MoCA

      iii. WAIS-IV DS, CD

      iv. Stroop A, B, & C

      v. Trails A & B

      vi. BNT

      vii. COWAT (FAS and Animals)

      viii. RCFT Copy and Immediate Recall

      ix. WMS LMI & LMII

      x. RAVLT

Primary Analysis

SPSS was used to analyze the data and an alpha of 0.05 was used for all statistical significant tests. Independent sample t-tests were conducted to determine whether significant differences in cognitive functioning can be observed been participants who endorse SSD symptoms of depression and those who do not endorse symptoms of depression. The independent variable was depression severity (Subsyndromal Symptomatic Depression and Non-depressed). The dependent variables were the neuropsychological measures included in the battery: WAIS-IV DS, WAIS-IV Coding, Stroop A & B & C, Trails A & B, BNT, FAS, Animals, Rey-O Copy and Immediate Recall, WMS-IV LMI & LMII, RAVLT, and FTT.

SPSS was used to analyze the data and an alpha of 0.05 was used for all statistical significant tests. A series of multiple linear regressions were conducted to evaluate which GDS subscales were the most important predictors of cognitive functioning. For each multiple regression, the independent variables were the GDS subscales: Dysphoric Mood, Withdrawal-Apathy-Vigor, Anxiety, Cognitive Impairment, and Hopelessness. Age, Education, and Gender were included in each model during Step 1 as controls. During Step 2, Hopelessness, Cognitive Impairment, Dysphoric Mood, Anxiety, and Withdrawal were included in the model. For the first analysis, the dependent variable was MoCA scores (Table 5). For the second analysis, the dependent variable was RAVLT immediate memory scores while for the third and fourth analyses the dependent variable was RAVLT short delay and RAVLT long delay, respectively. It should be noted that our data violated the assumption of normality. A square root transformation was performed to address this violation, however, the difference in results between the transformed and non-transformed data was negligible. While we will report the results for both our non-transformed (Table 5) and transformed data (Table 6), for interpretability's sake, we argue that interpretation of the data in its original form is the best mode of action.

RESULTS

Aim 1: Determine Whether Subsyndromal Symptomatic Depression

is Related to Cognitive Deficits.

Of the 106 participants, 84 were in the SSD group and 22 were in the non-SSD group. The two groups were similar in age, education, race, MMSE, and MoCA scores (Table 1). Independent samples t-tests were conducted to evaluate whether there were significant differences in cognitive performance between SSD and non-SSD participants. Cognitive test scores were reported as age-adjusted z-scores. A Bonferroni type adjustment was run to correct for multiple comparisons. On the RAVLT, there was a significant difference in the immediate recall over five learning trials (List A, Trials 1-5) between the SSD group (M=-0.14, SD=1.16) and the non-SSD group (M=0.89, SD=0.96, $t(104)=3.84$, $p < 0.001$). However, there were no significant differences between the two groups on the RAVLT after a delay nor were any significant differences observed on the WMS-IV LM—another measure of immediate (LM I) and delayed (LM II) memory. No other significant differences on any other measure of cognitive functioning were observed (Table 2).

Table 1. Demographic Characteristics of Depression Groups

Demographic Variables	SSD (n = 84) Mean (SD)	Non-SSD (n = 22) Mean (SD)
Age, Years	74.81 (8.28)	72.68 (7.19)
Education, Years	16.69 (2.56)	17.32 (2.61)
Gender (M/F)	36M/44F	10M/12F
Race, % Caucasian	84.80%	68.20%
MMSE	29.15 (1.14)	29.09 (1.07)
MMSE % Impaired	0	0
MoCA	25.50 (3.14)	25.27 (2.82)
MoCA % Impaired	42.50%	40.90%

Table 2. Neuropsychological Test Scores reported as age-adjusted z-scores for participants with and without depression symptoms

Neuropsychological Test	SSD (n = 84) Mean (SD)	Non-SSD (n = 22) Mean (SD)	P values
RAVLT Immediate	-0.14*** (1.16)	0.89*** (0.96)	p = 0.001
RAVLT SD	-0.20 (1.18)	0.37 (0.96)	p = 0.056
RAVLT LD	-0.05 (1.39)	0.43 (1.17)	p = 0.167
WMS-IV LMI	0.13 (0.97)	0.43 (0.71)	p = 0.291
WMS-IV LMII	0.14 (1.05)	0.41 (0.68)	p = 0.225
WAIS-IV DSF	-0.10 (0.83)	0.00 (1.00)	p = 0.954
WAIS-IV DSB	0.19 (0.93)	0.32 (1.04)	p = 0.587
WAIS-IV DSS	0.27 (0.89)	0.27 (0.66)	p = 0.998
WAIS-IV CD	0.10 (3.76)	0.50 (0.68)	p = 0.626
Stroop A	-0.99 (0.96)	-0.91 (0.88)	p = 0.984
Stroop B	-1.17 (0.91)	-1.09 (0.73)	p = 0.904
Stroop C	-0.54 (0.83)	-0.61 (0.84)	p = 0.614
Trails A	0.48 (1.09)	0.63 (0.85)	p = 0.728
Trails B	-0.51 (2.54)	-0.14 (1.15)	p = 0.541
BNT	0.17 (1.48)	0.61 (0.81)	p = 0.194
FAS	-0.35 (0.88)	-0.08 (0.69)	p = 0.148
Animals	0.10 (0.95)	0.23 (1.10)	p = 0.987
Rey-O Copy	-0.69 (1.38)	-0.48 (1.17)	p = 0.586
Rey-O Delay	0.40 (1.43)	0.42 (1.71)	p = 0.992
MoCA	25.44 (3.09)	25.27 (2.82)	p = 0.689
MMSE	29.14 (1.12)	29.09 (1.07)	p = 0.726

Note. ***p < 0.001.

Aim 2. Determine Whether Specific Symptoms of Depression

Are Specifically Tied to Cognitive Deficits.

Within our SSD group (N=84), Cognitive Impairment symptoms were the most commonly endorsed items, with 73.80 percent (N=62) of participants endorsing at least one item. Withdrawal-Apathy-Vigor symptoms were the second most commonly endorsed items, with 69.05 percent (N=58) of participants endorsing at least one item. Anxiety and Dysphoric Mood symptoms followed, with 19.05 percent (N=16) and 15.48 percent (N=13) of participants endorsing at least one item, respectively. Lastly, Hopelessness symptoms were the least endorsed items, with 7.14 percent (N=6) of the sample endorsing at least one item (Table 3).

Table 3. Summary of GDS and GDS Subscale Endorsement

Subscale (Total Possible Points)	N (%)	M (SD)
GDS (30)	84 (100)	3.65 (2.75)
Cognitive (3)	62 (73.80)	1.37 (0.61)
Withdrawal (5)	58 (69.05)	2.08 (1.23)
Anxiety (3)	16 (19.05)	1.31 (0.70)
Dysphoric (4)	13 (15.48)	1.69 (1.11)
Hopelessness (2)	6 (7.14)	1.17 (0.41)

A summary of Pearson's correlation coefficients for the five GDS subscales can be found in Table 4. Controlling for age, education, and gender, a multiple linear regression was conducted to evaluate which GDS subscales were the most important predictors of MoCA scores. When examining the non-transformed data, the final

regression model accounted for a significant proportion of the variance in MoCA scores, such that the optimal linear combination of all five depression subscales, age, education, and gender accounted for 30% of the variance in MoCA scores, R2adj = .30, $F(8,74)$ = 5.34, p < .01. Of the five subscales included in the model, Hopelessness, Dysphoric Mood, and Cognitive Impairment were significant predictors above and beyond the effects of age, education, and gender. Of the five subscales, Hopelessness was the most important predictor of MoCA scores, which accounted for 11.16% of the variance. As Hopelessness increased by one unit, MoCA scores decreased by .293 units, CI [-4.72, -0.99], p < .01. Dysphoric Mood accounted for 7.02% of the variance in MoCA scores. As Dysphoric Mood increased by one unit, MoCA scores decreased by .248 units, CI [-1.90, -0.16], p < .05. Cognitive Impairment accounted for 5.66% of the variance in MoCA scores. As Cognitive Impairment increased by one unit, MoCA scores increased by .404 units, CI [0.05, 1.66], p < .05. Anxiety and Withdrawal-Apathy-Vigor were not significant predictors (Table 5).

Table 4. Pearson's Correlation Coefficients for GDS Subscales

	Dysphoric	Withdrawal	Anxiety	Cognitive	Hopelessness
Dysphoric	1				
Withdrawal	0.43**	1			
Anxiety	0.09	0.05	1		
Cognitive	0.09	0.23*	0.19	1	
Hopelessness	0.11	0.05	-0.05	-0.01	1

Note. *p < 0.05, **p < 0.01

Table 5. Summary of Hierarchical Regression Analysis with non-transformed MoCA scores as the Dependent Variable

Depression Subscale	B	SE B	β	R	R²	ΔR²
Step 1				0.42	0.18	0.18***
Age	-0.11**	0.04	-0.30			
Education	0.28*	0.11	-0.24			
Gender	0.62*	0.30	0.20			
Step 3				0.59	0.34	0.16***
Age	-0.09**	0.03	-0.24			
Education	0.27*	0.11	0.23			
Gender	0.31	0.28	0.10			
Hopelessness	-2.90**	0.93	-0.28			
Dysphoric Mood	-1.02*	0.43	-0.23			
Cognitive Impairment	0.83*	0.38	0.22			
Anxiety	-0.46	0.49	-0.09			
Withdrawal	0.11	0.23	0.05			

Note. B = non-standardized coefficients; SE = standard error; β = standardized coefficients;
*p < 0.05; **p < 0.01; ***p < 0.001.

When examining the transformed data, the final regression model accounted for a significant proportion of the variance of the square root of MoCA scores, such that the optimal linear combination of all five depression subscales, age, education, and gender accounted for 29% of the variance in the square root of MoCA scores, R2adj = .29, $F_{(8,78)}$ = 5.02, $p < .01$. Of the five subscales included in the model, Hopelessness, Dysphoric Mood, and Cognitive Impairment were significant predictors above and beyond the effects of age, education, and gender. Of the five subscales, Dysphoric Mood

was the most important predictor of the square root of MoCA scores, which accounted

for 8.88% of the variance. As Dysphoric Mood increased by one unit, the square root of

MoCA scores decreased by .269 units, CI [-0.57, -0.08], p < .05. Hopelessness accounted

for 7.24% of the variance in the square root of MoCA scores. As Hopelessness increased

by one unit, the square root of MoCA scores decreased by .231 units, CI [-1.00, -0.08], p

< .05. Cognitive Impairment accounted for 5.95% of the variance in the square root of

MoCA scores. As Cognitive Impairment increased by one unit, the square root MoCA

scores increased by .228 units, CI [0.01, 0.40], p < .05. Anxiety and Withdrawal-Apathy-

Vigor were not significant predictors (Table 6). When RAVLT immediate memory,

RAVLT short delay, and RAVLT long delay were included as the dependent variable and

ran as three separate models, the results were no longer significant.

Table 6. Summary of Hierarchical Regression Analysis with transformed MoCA scores as the Dependent Variable

Depression Subscale	B	SE B	β	R	R²	ΔR²
Step 1				0.45	0.20	0.20***
Age	-0.03***	0.01	-0.35			
Education	0.08*	0.03	-0.28			
Gender	0.14	0.08	0.19			
Step 3				0.60	0.36	0.16***
Age	-0.02**	0.01	-0.27			
Education	0.08*	0.03	0.27			
Gender	0.06	0.08	0.08			
Hopelessness	-0.5*	0.23	-0.23			
Dysphoric Mood	-0.33*	0.12	-0.27			
Cognitive Impairment	0.21*	0.10	0.23			
Anxiety	-0.08	0.14	-0.06			
Withdrawal	0.04	0.06	0.07			

Note. B = non-standardized coefficients; SE = standard error; β = standardized coefficients;
*p < 0.05; **p < 0.01; ***p < 0.001

CHAPTER SIX

DISCUSSION

Our study provides two main contributions: (1) we identified significant differences in verbal learning and memory between SSD and non-SSD participants; and (2) we identified specific clusters of depression symptoms which are more closely tied to cognitive deficits.

Aim 1: Determine Whether Subsyndromal Symptomatic Depression is Related to Cognitive Deficits.

We intended to examine the relationship between SSD and cognitive ability in a sample of community-dwelling, healthy, older adults to determine whether significant differences in cognitive functioning could be observed between individuals who exhibited subthreshold depression symptoms and those who did not endorse symptoms of depression. After conducting a series of independent samples t-tests, we demonstrated that participants who endorsed subthreshold depression symptoms performed significantly worse on certain measures of cognitive functioning than participants who denied experiencing symptoms of depression. Specifically, we found differences in performance on the Rey Auditory Verbal Learning Test (RAVLT), which is a measure of verbal learning and memory (A. Rey, 1958). Briefly, the RAVLT consists of five presentations—or learning trials—of a 15-word list (List A, Trials 1-5) which is followed by an intervening interference list (List B) and then a subsequent free recall trial of the original list (List A, Trial 6). A delayed free recall trial (List A, Trial 7) is administered 20-30 minutes after the initial administration. Participants who endorsed subthreshold

depression symptoms performed significantly worse than participants who did not

endorse depression symptoms on the five learning trials (List A, Trials 1-5). This

corroborates our hypothesis that, even at the subthreshold level, depression symptoms

may have a significant impact on cognitive functioning. A possible explanation for our

SSD participants' inferior performance on the initial learning trials is that this task puts a

greater load on attention and concentration capabilities. During the initial learning trials,

the participant is instructed to retain and memorize a list of words for which they will

need to recall at a later time. Potentially, our participants who endorsed subthreshold

depression symptoms had more difficulty encoding new information than our participants

who did not endorse depression symptoms, hinting at the possibility of issues related to

attention.

Attention, in its most basic form, can be described as the ability to recognize and

respond to changes in the environment. In addition to orienting us, attention plays a

crucial role in memory as it is essential in encoding information into new memories

(Schoenberg & Scott, 2011). While several regions of the brain are involved in different

aspects of attention, it is within the frontal lobes that the bulk of our attentional processes

are located. The prefrontal cortex (PFC)—which is responsible for voluntary initiation of

attention—seems to be particularly important during the acquisition of new information.

Balthazar, Yasuda, Cendes, and Damasceno (2010) found the learning phase of the

RAVLT to be strongly related to the medial prefrontal cortex (MPC) while the medial

temporal lobes, specifically the hippocampus, are involved in the formation and storage

of memories. While the MPC seems to be associated with the selection, manipulation,

and maintenance of new information, it appears that the lateral prefrontal cortex (LPC) is

responsible for memory retrieval (Petrides, 2002). If we are to assume our SSD participants had underperforming medial prefrontal cortices with intact medial temporal lobes and lateral prefrontal cortices, this distinction—in part—may explain why we observed significant differences during the RAVLT learning trials (List A, Trials 1-5) but not during the delayed recall trials (List A, Trial 6 & 7).

To further clarify why our SSD participants may have had lower scores on tests associated with medial prefrontal cortices, brain-imaging studies of depressed patients have found consistent evidence of decreased neuronal volume of the PFC (Duman & Aghajanian, 2012). This decrease in size may be the result, in part, of acute and chronic stress associated with depression which has been shown to cause neuronal atrophy of the medial prefrontal cortex (Cowen, 2010; McEwen, Eiland, Hunter, & Miller, 2012). In fact, atrophy of the PFC pyramidal neurons can be observed in as little as one week after chronic stress exposure (Liu & Aghajanian, 2008). Further, PFC atrophy in healthy, undemented older adults was found to be a superior predictor of dementia conversion over a nine-year period than medial temporal lobe atrophy (Burgmans et al., 2009). Taking this into consideration, it is possible that even at the subthreshold level, the presence of depression symptoms has a significant impact on brain integrity and may increase risk of dementia conversion.

While the literature is limited, prior research has observed deficits on tests of memory, language, and executive functioning for SSD participants with cognitive complaints when compared with controls (Dillon et al., 2011; Gonzales et al., 2017). Our results are partially consistent with these findings. Specifically, Gonzales et al. (2017) found significant differences at baseline on the RAVLT immediate recall between SSD

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and non-SSD MCI participants. Further, Dillon et al. (2011) identified SSD participants with deficits on Logical Memory I (LMI)—a subscale of Wechsler Memory Scale-IV—which, like the RAVLT, is a measure of immediate memory. However, we did not observe differences in delayed memory, language, or other measures of executive functioning. These differences may be attributed to several factors. For instance, prior research has utilized participants with cognitive complaints and those already diagnosed with MCI while our participants were healthy individuals with no prior diagnosed cognitive disorders. Further, there appears to be slight differences in how we defined "subsyndromal depression". While Dillon et al. (2011) utilized the Beck Depression Inventory and excluded participants who scored below eight, we used the Geriatric Depression Scale and defined SSD as those who endorsed between one and nine symptoms which is below the clinical cutoff on the GDS and consistent with several previous studies (Gonzales et al., 2017; Mackin et al., 2012).

While previous literature has provided evidence for cognitive deficits in SSD participants with cognitive concerns, our results are novel in that we demonstrated that cognitive deficits can be observed in healthy, older adults who endorse at least one symptom of depression. Depression—specifically Major Depressive Disorder—has long been linked with cognitive impairment. Currently, there is evidence to suggest that MDD represents an independent risk factor for Alzheimer's Disease in early life while it may represent a prodromal stage of the disease in late life (Barnes et al., 2012; Ownby et al., 2006). The results of our study suggest that, even at the subthreshold level, depression may be a viable clinical marker for cognitive impairment. Implications of these results could mean utilization of the GDS—or other depression measures—as screeners for

individuals at risk for MCI/Dementia which may allow for early intervention. SSD treatment, in particular, is noteworthy as research has shown that the disorder is responsive to low-dose selective-serotonin reuptake inhibitors, problem-solving therapy, and exercise therapy (Brenes et al., 2007; Oxman et al., 2008; Tadić et al., 2010). Further, it is believed that roughly 15% of community-dwelling older adults and 50% of MCI patients qualify for SSD and that these individuals are at a 7-fold increased risk of developing MDD, highlighting the urgency and need for treatment (Geda et al., 2008; Goldney et al., 2004; Lyness et al., 2009). Early detection and treatment of SSD could potentially prevent worsening of depression symptoms as well as delay—or even curb— the manifestation of MCI/Dementia in later life.

Aim 2: Determine Whether Specific Symptoms of Depression
are Specifically Tied to Cognitive Deficits.

In addition to identifying differences in cognitive functioning between SSD and non-SSD participants, we aimed to determine whether specific symptoms of depression are more closely tied to cognitive dysfunction. We utilized the work of Adams et al. (2004) to categorize depression symptoms on the GDS into five distinct subscales: Dysphoric Mood, Withdrawal-Apathy-Vigor, Hopelessness, Cognitive Impairment, and Anxiety. It should be noted that our data violated the assumption of normality, which was to be expected, considering our population of interest were community-dwelling, healthy, older adults and high endorsement of depression symptoms was not anticipated. A square root transformation was performed to address this violation, however, the difference in results between the transformed and non-transformed data was negligible. For

interpretability's sake, we argue that interpretation of the data in its original form, with caution, is the best mode of action. However, after conducting a hierarchical linear regression, we demonstrated that depression symptoms related to Hopelessness, Dysphoric Mood, and Cognitive Impairment were significant predictors of MoCA scores—a commonly used measure of global cognitive functioning—above and beyond the effects of age, education, and gender. Specifically, we found that endorsement of symptoms related to Hopelessness and Dysphoric Mood were related to a decrease in cognitive performance while endorsement of Cognitive Impairment symptoms, paradoxically, were associated with improved cognitive functioning.

While depression has previously been linked to reduced cognitive functioning, our understanding of the specific symptoms related to these deficits are limited. Depression is heterogeneous in presentation, encompassing a wide array of symptoms including depressed/dysphoric mood, cognitive symptoms, somatic symptoms, and reduction in positive affect (Baune, Suslow, Arolt, & Berger, 2007). In fact, previous research has identified several distinct factors—or subscales—within depression screeners such as the GDS and CES-D (Adams et al., 2004; Brailean et al., 2016). The results of our study suggest that depression symptoms on the GDS related to Hopelessness and Dysphoric Mood may be predominately responsible for deficits in global cognitive functioning. The Hopelessness cluster consists of four items that deal with hopelessness, helplessness, and worthlessness. These feelings, in particular, have been shown to be predictive of suicidal ideation and behavior (Brown, Beck, Steer, & Grisham, 2000; Jeon et al., 2014; Lester & Walker, 2007). Taking this into consideration, the Hopelessness cluster may be important not only for screening cognitive dysfunction

but also assessing suicidal ideation or intent. The Dysphoric Mood cluster consists of nine items that detail depressed mood, emptiness, and a lack of happiness and satisfaction with life and is described by Adams et al. (2004) to be the "core of depressed mood" on the GDS. Our results are similar to previous research which identified the "Negative Affect" subscale on the 15-item GDS as predictive of a faster rate of decline in global cognition (Turner et al., 2015). The "Negative Affect" subscale shares many similarities with both our Hopelessness and Dysphoric Mood subscales—including items 4, 10, 17, 22, and 23—and can be considered the "core of depressed mood" on the 15-item GDS. Further, our Dysphoric Mood subscale shares many similarities with the Depressed Affect factor on the CES-D which has previously been linked to poor performance on a measure of non-verbal and abstract reasoning (Brailean et al., 2016).

While the results of our study suggest that Hopelessness and Dysphoric Mood clusters are related to reduced cognitive performance, endorsement of symptoms found within the Cognitive Impairment subscale were, oddly, associated with improved cognition. On the GDS, this cluster includes items that encompass confusion, difficulties with decision making, and reduced concentration. Though the results of our study appear counterintuitive, previous research has indicated that cognitive concerns are more closely linked to symptoms of depression and anxiety rather than objective cognitive decline (Cargin, Collie, Masters, & Maruff, 2008). In fact, patients diagnosed with MDD tend to underestimate their cognitive functioning while individuals with objective cognitive decline appear to have impaired awareness of their deficits and tend to overestimate their cognitive performance (Coutinho, Drummond, Teldeschi, & Mattos, 2016; Lehrner et al., 2015).

Symptoms on the GDS related to Cognitive Impairment were the most commonly endorsed items, with 74 percent of our sample endorsing at least one item within this cluster. This high level of endorsement is consistent with previous research which has found endorsement upwards of 75 percent in healthy, older adults (Ginó et al., 2010; João et al., 2016). With this in mind, it appears that complaints of impaired or declining memory are often reported despite any objective cognitive deficits. Further, there is evidence that suggests brief dementia screening tests—such as the MoCA—are not sensitive enough to detect impairment in cognitive functioning at the early stages of dementia in highly educated older adults (Geerlings, Jonker, Bouter, Adèr, & Schmand, 1999). Considering 69 percent of our sample had at least a Bachelor's degree, with 25 percent having obtained a doctorate, it is possible that any subjective cognitive complaints these individuals had were not detected on the MoCA. On the flipside, it is feasible to assume that our participants with impaired awareness of their cognitive deficits were less likely to endorse symptoms related to Cognitive Impairment. Taken together, this may explain why we observed improved functioning in our participants who endorsed symptoms within the Cognitive Impairment cluster.

The results of our study suggest that depression symptoms related to Hopelessness and Dysphoric Mood may be predictive of reduced cognitive functioning. While treating depression as a whole is certainly the goal, it may be efficacious to target symptoms related to Hopelessness and Dysphoric Mood in order to alleviate any cognitive dysfunction. Clinicians have long postulated that depression is not a monolithic disorder but rather a group of disorders which are heterogeneous in onset, symptoms, course, and treatment. While Dysphoric Mood symptoms—which includes feelings of

sadness, emptiness, and lack of satisfaction with life—may be described as the "core of depression", hopelessness has been identified as a possible subtype of depression which is aptly named hopelessness depression (Abramson, Metalsky, & Alloy, 1989). Research exploring the efficacy of treatment interventions—both psychotherapeutic and psychopharmacological—have shown promising results for both classifications of depression, suggesting interventions can be specifically tailored to address any cognitive concerns related to depression by way of Dysphoric Mood and Hopelessness symptoms (Driessen & Hollon, 2010; Handley et al., 2013).

In light of our findings in Aim 1—that there are significance differences in RAVLT immediate recall scores between our SSD and non-SSD participants—we also examined whether our depression subscales predicted RAVLT scores. We ran three separate models with RAVLT immediate recall, RAVLT short delay, and RAVLT long delay as our dependent variables. Unfortunately, none of these additional models were significant. Due to our findings in Aim 1, we had anticipated significance when RAVLT immediate recall was included in our model. Seeing as we did not observe significant differences among our SSD group, it is possible that the effect of depression on immediate verbal memory is only observed between depressed and non-depressed groups. This is to say that within a depressed group, the specific symptoms of depression have less of an effect on immediate verbal memory. Another possible explanation for our insignificant results is insufficient power. To further clarify, a multiple linear regression analysis—our analysis of choice for Aim 2—requires more power than the t-test we used in Aim 1. This suggests that our sample size, while sufficient for Aim 1, may not have been large enough to detect significance in Aim 2 when RAVLT immediate recall was

included in the model. It should be noted, however, that when RAVLT immediate recall was included, the GDS subscale Hopelessness was significant despite the overall model not being statistically significant. This is particularly noteworthy as Hopelessness was one of most significant predictors of global cognitive functioning when MoCA scores were used in our model. While we are unable to conclude that Hopelessness predicts RAVLT immediate recall scores, future studies with larger sample sizes may be able to further clarify the relationship between GDS subscales and RAVLT scores.

Limitations and Future Directions

Our study has several limitations. While there is evidence that suggests depression is a prodromal stage of dementia (Anstey et al., 2007), research has found that depressed patients exhibit greater cognitive impairment than healthy controls (Lim et al., 2013). While we were able to identify deficits in cognitive functioning amongst our SSD participants, whether these deficits are indicative of the prodromal stage of dementia or independently caused by depression is difficult to delineate with the cross-sectional design we employed. Future research should utilize a longitudinal study design that examines conversion rates of SSD to MCI/dementia to conclude that SSD represents a clinical marker of dementia. However, we have laid the necessary groundwork for future research to further examine this relationship.

A second limitation of our study is the non-normality of our data regarding symptom depression endorsement. As we utilized healthy, community-dwelling, older adults as our population of interest, we did not—nor did we expect to—observe high endorsement of depression symptoms on the GDS. However, when a square root

transformation was performed to address this violation, the difference in results between the transformed and non-transformed data was negligible. For interpretability's sake, we argue that interpretation of the data in its original form, with caution, is the best mode of action. With that said, future research should utilize a population with a more robust depression symptom endorsement in order to better elucidate the relationship depression subscales and cognitive functioning.

A third limitation of the current study includes the degree to which the results can be generalized to the greater population. The sample of interest consists solely of healthy, Seventh-day Adventists living in Southern California. There is evidence to suggest that religiosity protects against cardiovascular disease, which is a risk factor for dementia (Powell, Shahabi, & Thoresen, 2003). Further, the population of interest disproportionally resides in Loma Linda, California, which has been identified as a "Blue Zone"—or a region where people demonstrate measurably longer lifespans (Buettner, 2012). While there is research that suggest religiosity might provide better coping mechanisms to manage symptoms of depression over time (Amadi et al., 2016) which may affect longitudinal studies examining conversion rates, the current study only examined cross-sectional results. Regardless of the unique characteristics of our sample, the results of our analyses should provide basis for examination in other, more "representative" samples.

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