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White Matter Hyperintensities and Symptom Profiles of Late-Onset Depression: A Latent Class Analysis

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by

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Under the Direction of Vonetta Dotson, PhD

ABSTRACT

The vascular depression hypothesis, which posits that late-life depression may have a vascular origin, is supported by research findings of greater severity of white matter lesions in older adults with elevated depressive symptoms, reflected in white matter hyperintensities (WMH) on neuroimaging. Furthermore, WMH increases are more severe in individuals with late-onset depression and are associated with a distinct depressive symptom presentation. A growing body of work has focused on symptom-based approaches to understanding depression in older adults primarily using factor analytic methods to examine symptom dimensions of depression. However, few studies have used person-centered approach that may show subtle differences in symptom

profiles of depression among older adults. The current study aimed to identify symptom profiles of late-onset depression and explore associations with WMH using data from the large-scale National Alzheimer's Coordinating Center Data Set. Participants were 65 years and older, and without a history of depression in earlier life. Latent class analyses resulted in three qualitatively distinct symptom profiles – General Depression, Motivation/Withdrawal and Asymptomatic. The Motivation/Withdrawal symptom profile was associated with larger WMH volume compared to the General Depression and Asymptomatic symptom profile, but the comparison with General Depression was not significantly different. Results provide support for the idea that amotivation and withdrawal in later life may be more associated with vascular pathology. The current study findings highlight the importance and benefits of a symptom-based approach to depression in older adults.

INDEX WORDS: Late-life Depression, Late-onset depression, Subthreshold depression, White matter hyperintensities, Latent class analysis, Confirmatory factor analysis

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DEDICATION

"*Bringing the gifts that my ancestors gave, I am the dream and the hope…*"

Maya Angelou

This dissertation is dedicated to my grandmother for whom I am named who inspired in me a curiosity and passion for understanding aging. I have reached heights that she could not due to circumstance and I am eternally grateful for her love, support, prayers and inspiration.

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1 INTRODUCTION

According to global projections of mortality and burden of disease, by 2030 depression will be one of three leading causes of illness (Mathers & Loncar, 2006). In the United States alone, there has been a significant and rapid increase between 2005 to 2015 in one-year prevalence of depression in adults 50 years of age and older (Weinberger et al., 2018). While depression is less prevalent in older adults relative to younger adults, it results in significant and devastating consequences including increased risk of suicide, disability, high mortality and poor quality of life (Blazer, 2003). In an extensive review of the literature, Barnes and Yaffe (2011) found that depression was the second largest predictor of Alzheimer's disease cases in the United States, and fourth largest predictor globally. Several research studies have also reported that late-life depression is associated with a 2- to 5-fold increase in risk of dementia (Andersen, Lolk, Kragh-Sorensen, Petersen, & Green, 2005; Byers, Covinsky, Barnes, & Yaffe, 2012; Chen et al., 2008; Gatz, Tyas, St John, & Montgomery, 2005; Saczynski et al., 2010).

Despite extensive research and clinical efforts, depression remains poorly understood and treated in older adults, partially due to the heterogeneous nature of symptom presentations in depression. Growing evidence suggests that specific symptom-based differences in depression may be related to unique genetic, physiological and neurobiological factors, which impact prognosis and treatment (Hasler, Drevets, Manji, & Charney, 2004; Korszun et al., 2004). Neuroimaging studies examining symptom dimensions of late-life depression have been limited, but have documented distinct associations of different symptom dimensions with structural brain

differences in cortical brain regions (Dotson, Davatzikos, Kraut, & Resnick, 2009; McLaren et al., 2017) and with severity of white matter hyperintensities (WMH) in the brain (Kirton, Resnick, Davatzikos, Kraut, & Dotson, 2014). A systematic review found that white matter changes (as measured by WMH) were more common and severe in depressed relative to non-depressed older adults, with greater WMH burden in late-onset depression relative to early onset (Herrmann, Le Masurier, & Ebmeier, 2008).

In order to better understand distinct depression presentations, prior research has explored the association between white matter changes and depression at the symptom level using variable-centered, factor analytic approaches that yield symptom dimensions of depression (e.g., affective and somatic symptom dimensions). In contrast, person-centered approaches (e.g., latent class analysis) which identify groups of individuals with similar depression symptomatology (e.g., symptom profiles), have yet to be applied in research on white matter changes. The current study was designed to examine symptom profiles of late-life depression, with particular focus on late-onset depression; and to further examine associations with WMH.

1.1 Depression in Older Adults: An Overview

Depression is a highly heterogeneous disorder, with variability in symptom presentation across individuals. According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5; American Psychiatric Association, 2013), major depressive disorder (MDD) comprises of nine symptoms: (1) depressed mood, (2) anhedonia (diminished interest), (3) change in weight/appetite, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy, (7) feelings of worthlessness or inappropriate guilt, (8) diminished concentration or

decision-making, and (9) recurrent thoughts of death or suicidal ideation. To meet diagnostic criteria for MDD, an individual must exhibit at least five of the nine symptoms, of which at least one is either depressed mood or anhedonia (diminished interest). However, research suggests that there are qualitative (and quantitative) differences in the clinical presentations of depression in older adults. Relative to younger adults, older adults are less likely to endorse cognitive-affective symptoms of depression including depressed mood, one of the two required symptoms of depression according to DSM-5 criteria (Gallo, Rabins, & Anthony, 1999; Gallo, Rabins, Lyketsos, Tien, & Anthony, 1997), as well as, feelings of worthlessness and guilt (Balsamo, Cataldi, Carlucci, Padulo, & Fairfield, 2018; Fiske, Wetherell, & Gatz, 2009). Gallo et al. (1997) found that "depression without sadness" was twice as common as clinical depression in community-dwelling older adults, and further predicted mortality and both functional and cognitive impairment in a 13-year follow-up. The presentation of depression without dysphoria makes the identification of late-life depression particularly challenging due to the expectation of prominent depressed mood based on current diagnostic criteria.

Older adults frequently endorse depressive symptoms other than feelings of sadness. Somatic (e.g., fatigue, sleep disturbance, psychomotor retardation) and motivational (e.g., lack of interest or enjoyment, withdrawal) symptom endorsements are more characteristic of depression in older adults (Christensen et al., 1999; Hegeman, Kok, van der Mast, & Giltay, 2012). The prevalence of medical and physical morbidity that lead to somatic and functional changes increases with age; as such, the severity of somatic and motivational symptoms may be overestimated in the presence of somatic disease. However, studies have shown that somatic burden only increases the strength

of depressive symptoms rather than accounting for depression in this population (Hegeman et al. 2015; Scott et al. 2008). Older adults also frequently endorse feelings of hopelessness, which have been found to be the best predictors of suicide attempts in this population (Brodaty et al., 2001). Greater endorsement of subjective cognitive complaints (e.g., poor memory and concentration) are also characteristic of late-life depression, and objective neuropsychological measures have confirmed the presence of cognitive deficits in older adults with depression (e.g., executive dysfunction, slowed processing speed) (Butters et al., 2004).

Older adults also commonly present with elevated depressive symptoms that do not meet diagnostic criteria for a major depressive disorder (MDD) (Lyness et al., 2007; Meeks, Vahia, Lavretsky, Kulkarni, & Jeste, 2011) Subthreshold depression (also called subclinical or subsyndromal depression) in community-dwelling older adults is estimated at 12-30% relative to 2-5% for MDD (Steffens, Fisher, Langa, Potter, & Plassman, 2009). Subthreshold depression is associated with similar clinically important outcomes as MDD including decreased physical functioning, more disability days, low social support, and cognitive difficulties (Hybels, Blazer, & Pieper, 2001; Lavretsky & Kumar, 2002; Meeks et al., 2011). There is also evidence that subthreshold depression is similarly related to structural brain changes that resemble those linked to major depression (Besteher, Gaser, & Nenadić, 2019).

A number of studies have also documented differences in the presentation of depression in older adults based on age of onset. The term late-life depression refers to the presence of depressive symptoms in older adulthood (Grayson & Thomas, 2013). There is variability in age cutoffs defining older adulthood across studies; cutoffs are

generally set at around 65 years (±5 years), but some studies include individuals as young as 50-55 years old. Late-life depression can further be dichotomized by age at which the first depressive episode occurred: early-onset and late-onset depression. Early-onset depression refers to the presence of depressive symptoms prior to older adulthood and may represent a recurring course of depression in older adults; whereas late-onset depression is defined as depressive symptoms emerging for the first time in older adulthood (Mitchell & Subramaniam, 2005).

There is evidence that late-onset depression may be characteristically different from early-onset depression, particularly with respect to neurobiological etiology, symptomatology, and neuropsychological outcomes (Krishnan, 2002; Rapp et al., 2005). For example, late-onset depression is characterized by more pronounced attention and executive deficits, slowed processing speed (Herrmann, Goodwin, & Ebmeier, 2007), and greater likelihood of progression to dementia (Richard et al., 2013). Individuals with early-onset depression are more likely to have a family history of depression, suggesting greater genetic heritability in this population (Jellinger, 2013). Furthermore, MRI findings have identified structural brain differences between late- and early-onset depression. Cerebrovascular disease (e.g., ischemic small-vessel disease) is considered in the pathogenesis of late-onset depression with imaging studies consistently showing changes in white matter hyperintensities in this sub-group of older adults with depression (Sneed & Culang-Reinlieb, 2011). In a meta-analysis of 54 studies of late-life depression, Salo and colleagues (2019) found that WMH burden was more pronounced in older adults with late-onset depression than early-onset depression, or than non-depressed older adults. Early-onset depression, on the other

hand, is commonly associated with significant hippocampal volume loss suggested to be related to decreased hippocampal neurogenesis due to recurrent depressive episodes (MacQueen & Frodl, 2011).

1.1.1 Vascular Depression Hypothesis

In 1905, Guapp and colleagues proposed the concept of arteriosclerotic depressive disease, based on clinical evidence of depressed mood from cerebrovascular damage (Gaupp, Berrios, & Pomarol-Clotet, 2000). Elaborating on this concept, Alexopoulos and colleagues (1997) proposed the vascular depression hypothesis which argues that cerebrovascular disease may “predispose, precipitate or perpetuate” depressive symptoms. They suggest that an accumulation of small vascular insults/lesions in the brain could eventually reach a threshold level causing a predisposition to depression. In other words, vascular abnormalities may increase older adults’ vulnerability to subsequent depression, with the presence of adverse psychosocial stressors (e.g., negative life events, poor social support) contributing to the onset of depression in the context of this vascular predisposition, as illustrated in Figure 1.1.

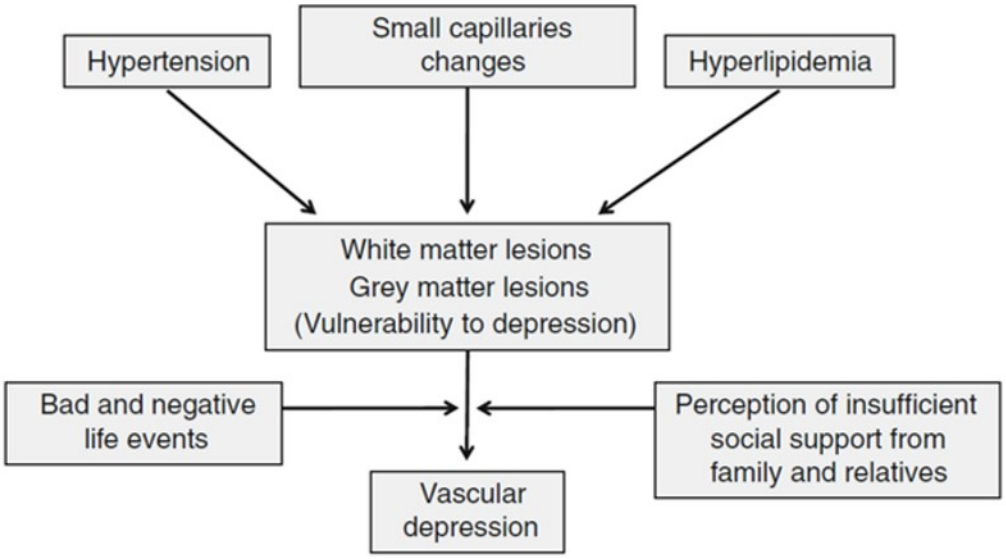

Figure 1.1 Model of the vascular depression illustrated by Aizenstein et al. (2016)

Cerebrovascular risk factors or cerebrovascular diseases are considered one of the cardinal features of vascular depression. The vascular depression hypothesis is supported by findings of a greater prevalence of depression in individuals with vascular risk factors such as hypertension, diabetes mellitus, coronary artery disease, and stroke compared to other medical populations (Aizenstein et al., 2016; Armstrong et al., 2017; Mast et al., 2008; Scott & Paulson, 2018). The presence of MRI markers of cerebral small vessel disease (e.g., WMH, subcortical infarcts, microbleeds, lacunes, arterial stiffness) are commonly observed in late-life depression (Feng, Fang, Xu, Hua, & Liu, 2014; Santos et al., 2009; Wu, Li, Tan, Liu, & Huang, 2014). However, some neuroimaging and neuropathology studies have not found a relationship between vascular abnormalities and depression (Kales, Maixner, & Mellow, 2005; Santos et al., 2010). Nonetheless, the current consensus is of a pathogenic contribution of vascular abnormalities to late-life depression, particularly late-onset depression. However, the relationship between vascular abnormalities and depression is considered bi-directional

(Alexopoulos 2019). Studies have shown that a history of depression increases the risk of vascular disease and stroke, and a worsening course of depression may occur following the onset of vascular disease (Pan et al., 2012; Thomas, Kalaria, & O'Brien, 2004).

In addition to white matter changes, vascular depression is associated with gray matter reductions in frontal-subcortical brain structures (including the anterior cingulate, orbitofrontal and medial frontal cortices, hippocampus, amygdala) (Aizenstein et al., 2016; Culang-Reinlieb et al., 2011). These volumetric reductions along with WMH suggest that disruptions in fronto-striatal-limbic circuitry are involved in vascular depression. WMH may impact white matter tracts (e.g., cingulum, uncinate fasciculus, and superior longitudinal fasciculus), resulting in disconnection and dysfunction of brain circuits supporting affective and cognitive functioning (Taylor, Aizenstein, & Alexopoulos, 2013).

Clinically, vascular depression is best characterized by later age of initial depression onset, psychomotor slowing, motivational symptoms (i.e., loss of interest, initiative), apathy, absence of family history and presence of cardiovascular illness (Grool et al., 2013; Naarding et al., 2016; Naarding et al., 2007). Cognitive difficulties, including slowed processing speed and executive dysfunction in particular, are common, and are often associated with severity of functional disability in this population (Lugtenburg et al., 2017; Morimoto, Kanellopoulos, Manning, & Alexopoulos, 2015; Sheline et al., 2006).

1.1.2 Symptom-Level Approaches to Late-Life Depression

Symptom-level approaches to depression focused on investigating patterns of individual symptoms are an alternative to the use of current DSM-5 diagnostic criteria. These approaches rely on identifying patterns of depression symptoms typically using depression symptom inventories.

Factor analytic studies have identified several stable symptom dimensions of depression. In late-life depression, negative affect, lack of positive affect, somatic, and interpersonal relationship symptom dimensions have been reported based on factor analysis of the Center for Epidemiologic Studies Depression (CES-D) scale (Hybels, Blazer, Landerman, & Steffens, 2011; Hybels, Blazer, Pieper, Landerman, & Steffens, 2009). The Beck Depression Inventory (BDI) has typically yielded cognitive-affective and somatic symptom dimensions in older adults (Segal, Coolidge, Cahill, & O'Riley, 2008; Steer, Rissmiller, & Beck, 2000). Hegeman et al. (2012) reported mood, motivation and somatic symptom dimensions on the Inventory of Depressive Symptomatology Self Report (IDS-SR) in older adults. Three symptom dimensions have been identified on the Montgomery-Asberg Depression Rating Scale (MADRS) including dysphoric apathy/retardation, psychic anxiety, and vegetative symptoms (sleep, appetite) (Parker, Flint, Bosworth, Pieper, & Steffens, 2003).

In a meta-analysis, Hegeman et al. (2012) found that older adults endorsed more somatic symptoms than younger adults, which was associated with a higher burden of somatic disease (Hegeman, de Waal, Comijs, Kok, & van der Mast, 2015). They suggested that the presence of higher somatic disease burden in late-life depression may be a consequence of misattribution of symptoms of chronic somatic impairment

and physical problems to depression. Moreover, the severity of depressive symptoms may be overestimated in older adults because of comorbid physical problems and underestimated in those with less somatic symptoms due to the tendency to under-report depressive symptoms (e.g., mood & motivational symptoms). However, other studies have found somatic symptoms of late-life depression even after adjusting for the presence of chronic and physical diseases (Schaakxs, Comijs, Lamers, Beekman, & Penninx, 2017). The Geriatric Depression Scale (GDS) was designed specifically for older adults and does not include any somatic/vegetative items that are likely comorbid with medical disorders (Montorio & Izal, 1996; Yesavage et al., 1982).

The Geriatric Depression Scale (GDS) is widely used in both clinical and research settings to assess depression severity in older adults. The original GDS consisted of 30 items, but it has subsequently been shortened to a 15-item measure (GDS-15) to improve ease of administration (Sheikh & Yesavage, 1986), and is the most widely used scale for assessing late-life depression (Balsamo et al., 2018; Mahapatra, Sharma, & Khandelwal, 2015). In a meta-analysis of 25 studies (*N* = 14,669*)* of exploratory factor analysis of the 30-item GDS, Kim et al. (2012) found that the most common symptom dimensions were dysphoria, social withdrawal/apathy, and reduced positive mood. In contrast, limited studies have explored the symptom dimension of the GDS-15 specifically. The first factor analysis of the GDS-15 included a sample of community-dwelling older adults and yielded a three-factor structure including general depressive affect (seven items), life satisfaction (four items), and withdrawal (three items), with one item (related to memory impairment) failing to fit into any of the factors (Mitchell, Mathews, & Yesavage, 1993). Since then other studies using factor

analysis have resulted in a range of two to five symptom dimensions on the GDS-15, with differences noted across diagnostic groups. Table 1.1 provides a brief summary of existing studies of factor analysis of the GDS-15.

Table 1.1 *Factor Structure of the GDS-15 Summary*

Study	Analysis	Population	Participants Mean age (Range)	Number of Factors 1	2	3	4	5
Two-factor								
Brown et al. (2007)	EFA/ CFA	Cognitively Intact/ Clinical	*n* = 294 68.65 years (43 to 91 years)	General Depression Affect (2,3,4,6,8,9,12,14,15, 10)	Life Satisfaction (1, 5,7,11, 13)	--	--	--
Friedman et al. (2005)	EFA	Cognitively intact/ Community-dwelling	*n* = 960 79.3 years (65-100 years)	Depression (2, 3, 4, 6, 8,9,10, 12,13,14,15)	Positive Affect (1,3,5,6,7,11)	--	--	--
Three-factor								
Shahnawaz et al. (2013)	PCA	Cognitively Intact/ MCI/ Community-dwelling	*n* = 767 78.53 years (70-90 years)	Mood (6,8,10,12,14,15)	Positive affect (1, 5, 7)	Motivation (2, 9, 13)	--	--
Mitchell et al. (1993)	NR	Community-dwelling	*n* = 868 74.8 years (65-101 years)	General Depressive Affect (3,4,6,8,12,14,15)	Life Satisfaction (1,5,7,11)	Withdrawal (2,9,13)	--	--
Weintraub et al. (2007)	PCA	PD	*n* = 187 68.2 years (NR)	Factor 1 (1,3,5,7,8,11,12,14,15)	Factor 2 (4,6,8,10,12,14,15)	Factor 3 (2,9,13)		
Five-factor								
Weintraub et al. (2007)	PCA	AD	*n* = 232 76.0 years (NR)	Factor 1 (1, 5, 7,13)	Factor 2 (3,4,12,15)	Factor 3 (8,12,14)	Factor 4 (6, 10,11)	Factor 5 (2, 9)

NR – not reported, EFA – exploratory factor analysis, PCA – principal component analysis, LCA – latent class analysis, MCI – Mild cognitive impairment, PD – Parkinson's Disease, AD- Alzheimer's disease, GDS-15 item numbers are in parentheses

1.1.2.1 Latent Variable Mixture Modeling Approaches

A different approach to using factor analysis to identify subtypes of depressive symptoms in older adults is the use of latent class analysis (LCA) or latent profile analyses (LPA). In contrast to factor analysis, which identifies latent factors based on the relationships between variables (e.g., items on a symptom inventory), LCA and LPA identify subgroups of individuals based on homogenous patterns across variables (e.g., similar patterns of symptom endorsement on a depression inventory) (Nylund-Gibson & Choi, 2018). Symptom combinations identified using LCA and LPA are referred to as symptom profiles.

A few studies in older adults have used mixture modeling approaches to identify symptom profiles of depression. Studies have yielded symptom profiles distinguished primarily by severity of depression. In a study of 366 older adults (aged ≥ 60 years) with major depression based on DSM-IV criteria, across both in-patient and out-patient settings, Hybels et al. (2011; 2009) identified three latent classes on the Hamilton Rating Scale for Depression (HAM-D) and four latent classes on the CES-D and Montgomery-Asberg Depression Rating Scale (MADRS) all separated by severity of depression ranging from few, moderate, less severe to more severe depressive symptoms. In a sample of community-dwelling older adults (aged ≥ 65 years), Hybels et al. (2013) again identified four latent classes on the CES-D separated by severity, even though this sample was demographically different from prior studies (e.g., predominantly Black, less than 12 years of education and participants without major depression).

Other studies have identified symptom profiles separated by both severity and specific symptom dimensions of depression in community-dwelling older adults. In a sample of 400 older adults (aged ≥ 65 years) with a current depressive episode, Lee et al. (2012) using a modified version of the depression module of the Diagnostic Interview Schedule identified three classes: a class consisting of high endorsement of all symptoms (“major depression”), a class with high endorsement of sadness and low endorsement of other depressive symptoms (“minor depression”), and a class with higher endorsement of somatic symptoms (i.e., psychomotor changes, sleep disturbance, and fatigue) and sadness but no endorsement of loss of interest. Mora et al. (2012) identified a four-class model using latent profile analysis of the CES-D (aged ≥ 56 years, *N* = 420). Results identified a “high depression symptoms” class consisting of high endorsement of most symptoms and CES-D total score within the clinical range, a “low depression symptoms” class consisting of low endorsement of all items and low overall CES-D score, a “subthreshold with anhedonia” class characterized by high endorsement of lack of positive affect and moderate endorsement of somatic complaints, with only 35% of the class falling within the clinical range on the CES-D, and a “subthreshold with anhedonia and negative interpersonal feelings” which is characteristically similar to the “subthreshold with anhedonia” class with the exception of a greater endorsement of negative interpersonal feelings and 45% within the clinical range on the CES-D. In a sample of older adults enrolled in The Health and Retirement Study (HRS) (aged ≥ 65 years, of *N* = 3665), Lohman and colleagues (2014) using the 8-item CES-D, found three classes separated by severity (severe, moderate, low) and a “somatic depression” class characterized by higher endorsement of restless sleep, lack

of motivation, and feeling activities were an effort. Interestingly, despite the prevalent use of the GDS-15 to assess depression in older adults, there have been no studies using LCA or LPA approaches to identify symptom profiles in late-life depression.

Across these studies, results have shown variability in symptom profiles, with clinical samples being primarily driven by depression severity, while community-dwelling samples may be best characterized by both depression severity and specific symptom dimensions (particularly somatic or motivational symptoms). Variable findings may be related to study characteristics: clinical vs non-clinical populations, differences in cutoff for age of older adulthood, and inclusion of individuals with cognitive impairment in some studies. An important factor to consider is the conflation of early- and late-onset depressive symptoms in these studies given evidence that depressive symptoms initially appearing in later life are symptomatically and etiologically distinct from early-onset depressive symptoms. Mixture modeling approaches may be useful for investigating symptom profiles in late-onset depression as this sub-group is posited to have a very specific symptom presentation (i.e., motivation symptoms, psychomotor slowing) (Power, Greene, & Lawlor, 2017).

1.2 White Matter Hyperintensities in Late-Life Depression

1.2.1 What are White Matter Hyperintensities?

The brain's white matter consists of myelinated axons that combine to form tracts connecting different cortical and subcortical gray matter into coherent neural networks (Filley, 2012). In contrast to the brain's gray matter, which mediates information processing, white matter aids in information transmission via a bidirectional informational transfer highway. WMH are abnormalities of the white matter that appear

bright (i.e., hyperintense) on magnetic resonance imaging (MRI) (Huettel, Song, & McCarthy, 2004). WMH tend to accompany cerebrovascular disease (cerebral small vessel disease, hypertension, coronary artery disease), and is frequently observed in advanced age (Breteler et al., 1994; Gattringer et al., 2012; Hendrie, Farlow, Austrom, Edwards, & Williams, 1989). WMH are presumed to reflect silent vascular lesions in the brain (Wang, Leonards, Sterzer, & Ebinger, 2014); however, the exact etiology and pathogenesis of WMH are not fully understood, but are considered multifactorial (e.g., changes in cerebrospinal fluid, microglial inflammation).

WMH, or leukoaraiosis, were first identified by Hachinski and Merskey (1987) based on observations of cerebral white matter changes in older adults with or without signs of cerebral impairment. Broadly, WMH are attributed to vascular origins, and are considered a feature of small vessel disease (Wardlaw, Valdés Hernández, & Muñoz-Maniega, 2015). Small arteries (arterioles) arising from larger arteries provide blood supply to cerebral white matter. These arterioles are less interconnected (i.e., anastomose) with surface blood vessels and have limited collateral supply making them vulnerable to systemic or focal decreases in cerebral blood flow (Pantoni & Garcia, 1997). Chronically reduced cerebral blood flow is related to arteriolosclerosis (i.e., thickening of the vessel wall and narrowing of the vascular lumen) which is strongly linked with cardiovascular illness such as chronic hypertension. Chronic reduction in cerebral blood flow can lead to hypoxia, altered cerebral autoregulation, breakdown of the blood-brain barrier, increased release of proinflammatory protein into vessel walls and brain parenchyma resulting in white matter changes (Merino, 2019). The resulting lesions to the white matter are observed on MRI as bright spots and are termed white

matter hyperintensities (WMH). In other words, WMH are localized signals of widespread changes in white matter.

1.2.2 Relationship between WMH and Late-Life Depression

Robust evidence indicates that white matter abnormalities are associated with late-life depression. Neuroimaging studies have reported the presence of compromised white matter in late-life depression that is more severe than that seen in non-depressed older adults (Casanova, Starkstein, & Jellinger, 2011; Wen, Steffens, Chen, & Zainal, 2014). Greater longitudinal increases in WMH volume are associated with more persistent depressive symptoms (Taylor et al., 2003), particularly in late-onset depression (Herrmann et al., 2008; Nebes et al., 2002). White matter changes pre-date and predict late-life depression (Teodorczuk et al., 2007); however, the relationship is likely bidirectional.

Several systematic and meta-analytic reviews have reported significant cross-sectional and longitudinal associations between WMH and depression in older adults (Thomas et al., 2004; van Agtmaal, Houben, Pouwer, Stehouwer, & Schram, 2017; Wang et al., 2014). In addition, Herrmann et al. (2008) reported a four-fold higher prevalence of WMH in late-onset depression relative to early-onset and non-depressed older adults. In a more recent meta-analysis of 68 studies, Salo and colleagues (2019), also found a strong association between late-onset depression and increased WMH relative to early-onset depression.

A few studies have explored the association between symptom dimensions of depression and white matter changes (Table 1.2). Findings suggest that reduced white matter integrity is associated with depressed mood, anhedonia, apathy, and somatic

symptoms in late-life depression. The majority of these studies focused on late-life depression broadly, with only one investigating WMH associations with symptom dimensions of late-onset depression. Tully et al. (2017) reported associations with depressed mood and low positive affect symptoms, depending on location of WMH, in late-onset depression.

Table 1.2 *White Matter Integrity and Depression Symptom Dimensions Summary*

STUDY	Demographics	Measure	KEY FINDINGS
Lavretsky et al. (2008) Quantified WM volumes, lacunar volumes in WM, WMH volume	>55 years LLD Community-dwelling	MUDS	**Cross-sectional**: Larger volume of lacunes in the white matter was associated with depressed mood, anhedonia, anergia and apathy; Smaller white matter volume was associated with anhedonia, anergia, and apathy; Greater WMH volume was associated with anergia and anhedonia.
Dotson et al. (2009) Quantified WM volumes	≥56 years LLD Community-dwelling	CES-D	**Longitudinal**: Faster rate of left frontal white matter volume decline associated with higher depressed mood symptoms.
Dotson et al. (2013) WMH ratings	55-85y (baseline) LLD Community-dwelling	CES-D	**Longitudinal**: Total CES-D and depressed mood dimension were not associated with WMH in total sample. Depressed mood symptoms predicted increased WMH in men, but not women (study did not examine other subscales of the CES-D)
Kirton et al.(2014) Quantified WML volumes	≥60 years LLD Community-dwelling	CES-D	**Cross-sectional**: Depressed mood and somatic symptoms associated with WML volume in men, but not women; Total CES-D score associated with WML volumes in women, but not men **Longitudinal**: Depressed mood and somatic symptoms associated with increased WML volumes in total sample; Total CES-D score, and somatic symptoms associated with faster rate of increase in WML volume in women, but not men
Tully et al. (2017) Quantified WMH	65-80 years LOD Community-dwelling	CES-D	**Longitudinal**: Periventricular WMH volume associated with low positive affect among incident depression; Deep WMH volume associated with depressed affect among incident depression; Deep, periventricular and total WMH associated with interpersonal problems in those who developed dementia with depression

Note: WM- white matter; WMH – white matter hyperintensities; WML- white matter lesion; LLD- late-life depression; LOD- late-onset depression; MUDS- Minimum Uniform Dataset; CES-D- Center for Epidemiologic Studies Depression.

1.3 The Current Study

Our current understanding of depression is stymied by heterogeneity in symptom presentations which obfuscate important differences in individuals with depression. In particular, older adults with depression show symptomatic differences including less prominent depressed mood, greater somatic and motivational symptoms, and are less likely to meet diagnostic criteria for major depression. Moreover, symptomatic and neurobiological differences are also observed based on age of initial depressive symptom onset (early- vs late-onset depression). The vascular depression hypothesis posits that vascular abnormalities are associated with depression in older adults. And while the vascular depression hypothesis does not make a distinction between early versus late onset of illness, growing evidence suggests that a late-onset depression profile may better fit the vascular depression hypothesis (Salo et al., 2019; Taylor, Schultz, Panaite, & Steffens, 2018).

Although studies have focused on exploring the relationship between WMH (a marker of cerebrovascular pathology) and late-onset depression, little work has focused on combining a symptom-level approach to late-onset depression in investigations of white matter changes. The overall goal of the current study is to examine late-onset depression at the symptom-level and further investigate associations between specific symptom profiles and white matter changes (WMH).

Clinically, improving our understanding of depression symptom presentations in older adults will aid in adequate identification of depression in this population as depression is typically under-recognized by both medical professionals and older adults who may associate depression with sadness, or attribute symptoms to a normal aging process (Gum, McDougal, McIlvane, & Mingo, 2009). A symptom-level approach may

aid in better identification older adults who have clinically meaningful depressive symptoms but do not meet conventional diagnostic criteria for clinical depression. Furthermore, a better understanding of the symptom profiles linked to vascular etiology increases our theoretical understanding of vascular depression and may also inform tailored treatment considerations and planning.

1.3.1 Specific Aims and Hypotheses

Aim 1: The first aim of the current study was to identify symptom profiles of depression in a sample of community-dwelling older adults, by conducting a latent class analysis (LCA) of the GDS-15. Symptom profiles were hypothesized to mirror symptom dimensions on the GDS-15, based on some consistency in item loadings across previous factor analytic studies of this measure (Table 1.3). The proposed symptom profiles included: 1) depressed mood, 2) lack of positive affect, 3) motivation/withdrawal. To confirm the validity of the proposed latent constructs, a confirmatory factor analysis was conducted prior to the LCA.

Table 1.3 Hypothesized latent classes on the GDS-15 by items

Depressed mood	Positive affect	Motivation
3. Do you feel that your life is empty? 4. Do you often get bored? 6. Are you afraid that something bad is going to happen to you? 8. Do you often feel helpless? 12. Do you feel pretty worthless the way you are now? 14. Do you feel that your situation is hopeless? 15. Do you think that most people are better off than you are?	1. Are you basically satisfied with your life? 5. Are you in good spirits most of the time? 7. Do you feel happy most of the time? 11. Do you think it is wonderful to be alive now?	2. Have you dropped many of your activities and interests? 9. Do you prefer to stay at home, rather than going out and doing new things? 13. Do you feel full of energy?

Note. GDS-15 – Geriatric Depression Scale, short form

Aim 2: The second aim of the current study was to investigate differences in volume of white matter hyperintensities (WMH) between symptom profiles of late-onset depression. Evidence from the literature suggest that vascular depression is related to greater motivational and anhedonic mood disturbance relative to depressed mood (Alexopoulos, 2019), with this profile more likely to be characteristic of late-onset depression (Salo et al., 2019). Therefore, it was hypothesized that WMH volume would differ between depressed mood, positive affect and motivation/withdrawal symptom profiles, with the latter demonstrating greater WMH burden consistent with a vascular depression profile. In other words, the motivation/withdrawal was expected to have a significantly higher mean WMH volume relative to the other two classes.

Aim 3: The third aim was to assess the impact of clinical diagnosis on the relationship between WMH and symptom profiles of late-onset depression. The sample was stratified by clinical diagnosis – clinical depression, or subthreshold depression – to investigate whether subthreshold depression had the same WMH and symptom profile relationship as clinical depression. It was expected that results would be similar between clinical and subthreshold depression in this sample.

2 METHOD

2.1 Participants

The current study utilized archival data from the National Alzheimer's Coordinating Center (NACC) data repository. The NACC is a publicly available standardized, large-scale dataset with clinical and imaging data from approximately 39 past and present National Institute of Aging (NIA) funded Alzheimer's Disease Centers (ADCs) across the Unites States. In 2005, ADCs began collecting longitudinal demographic, clinical, neuropsychological, diagnostic and genotype data on participants to a common

database, known as the NACC-Uniform Data Set (UDS). In 2013, a subset of ADCs began to voluntarily collect structural MRI images on participants enrolled in NACC-UDS, with currently 19 sites contributing MRI data to NACC (Beekly et al., 2007; Besser et al., 2018). A formal data request was submitted to NACC for this study. Access was granted with approval following a brief data use description and completion of a data use agreement. The dataset included data from September 2005 (the earliest time of UDS data availability) to the June 2019 NACC "data freeze." All NACC data were stored without personal identifiers.

The dataset for the current study was restricted to participants who completed both the NACC-UDS and MRI visits. Specific inclusion and exclusion criteria for the current study are outlined in Table 2.1. In this study, older adulthood was designated as 65 years and older based on age cutoffs consistent with The National Institute on Aging: Strategic Directions for Research (NIA, 2020). To exclude participants with a history of early-onset depression, participants who reported a history of depressive episodes prior to age 65 where excluded. The NACC-UDS variables DEP2YRS and DEPOTHR, measuring active depression in the past two years, and presence of depression episodes more than two years ago, respectively, were used.

Table 2.1 *Inclusion and exclusion criteria*

Inclusion Criteria	Exclusion Criteria
1. Age ≥ 65 years 2. Cognitively Intact 3. No history of depression before age 65 **4.** Have brain imaging visit within one year of a UDS visit	1. Presence of neurodegenerative disorders (Lewy Body, frontotemporal dementias), other brain diseases (e.g., cancer, amyotrophic lateral sclerosis, severe TBI), and chronic medical illness (e.g., HIV, metastatic cancer) 2. Current or past major psychiatric disturbance apart from depression (e.g., bipolar disorder, schizophrenia, alcohol and/or substance abuse)

2.2 Procedure

Participants were recruited in a variety of ways including clinician referral, self-referral by patients or family members, and active recruitment through community organizations. The recruitment, consent, and data collection protocol was described in detail by Morris et al. (2006). At each annual NACC-UDS visit, participants completed a standardized visit packet including basic sociodemographic information, personal and family medical history, and self-report and collateral questionnaires. They also received psychiatric and neurological examinations, and neuropsychological measures. Clinical diagnosis of cognitive status was determined by a multidisciplinary consensus conference or diagnosis by an individual clinician according to NACC UDS protocol. A subset of participants also received brain imaging. The NACC databases are approved by the University of Washington Institutional Review Board, and informed consent from participants was obtained at the individual ADCs under local institutional review board oversight.

The NACC provided separate SPSS data files for the NACC-UDS and imaging data. For the purposes of this study, both data files were combined, using the unique participant identifier assigned to each participant. Based on the inclusion criteria, participants with brain imaging and UDS visit data within a one-year period were retained in the new combined dataset. Using this combined dataset, the remaining inclusion and exclusion criteria were applied to the data. This combined dataset was used for data analysis in the current study.

2.3 Measures

Sociodemographic (i.e., age, race, sex, education level), neuroanatomical and depression variables of interest from the broader NACC data repository were used in

the current study. Full descriptions of all measures, including measures not included in this study, have been described elsewhere (Besser et al., 2018; Weintraub et al., 2018).

2.3.1 Depression Variables

Geriatric Depression Scale-15 item (GDS-15). The GDS-15 was used to assess depression symptomatology (Table 2.2). The GDS-15 is a 15-item dichotomous (yes/no) self-report depression symptom inventory developed specifically for older adults (Sheikh & Yesavage, 1986). Each item is scored 0 or 1 yielding a total score of 0 to 15 points. For 10 items on the GDS-15, a score of 1 (yes) indicates the presence of the depressive symptom, and for the remaining five items a score of 0 (no) indicates the presence of the depressive symptom. A recent systematic review found a sensitivity of 0.89 and specificity of 0.77 for a clinical cut-off score of 5 (Pocklington, Gilbody, Manea, & McMillan, 2016). The GDS-15 was developed from the original 30-item GDS (Yesavage et al., 1982) to reduce the interference of fatigue and concentration difficulties on questionnaire completion in older adults (Sheikh & Yesavage, 1986). The GDS-15 has been found to have excellent reliability, validity and clinical utility, similar to the original GDS (Balsamo et al., 2018). Participants completed the GDS-15 either independently or with assistance from the ADC staff (Chopra, Sullivan, Feldman, Landes, & Beck, 2008).

Clinical Diagnosis of Depression. During the NACC-UDS visit, the participants and their collateral sources were jointly interviewed by an ADC clinician using a semi-structured interview format (Form B9: Clinician Judgement of Symptoms). The clinicians made a clinical diagnosis of major depression during the evaluation based on the *Diagnostic and Statistical Manual of Mental Disorders* criteria, using either the Fourth (DSM-IV) or Fifth (DSM-5) Editions, depending on study visit date. The clinical

diagnosis was made without prior knowledge of the participants' GDS-15 ratings during the visit (Chopra et al., 2008).

Table 2.2 *Geriatric Depression Scale (GDS-15)*

	Yes	**No**
1. Are you basically satisfied with your life?	0	1
2. Have you dropped many of your activities and interests?	1	0
3. Do you feel that your life is empty?	1	0
4. Do you often get bored?	1	0
5. Are you in good spirits most of the time?	0	1
6. Are you afraid that something bad is going to happen to you?	1	0
7. Do you feel happy most of the time?	0	1
8. Do you often feel helpless?	1	0
9. Do you prefer to stay at home, rather than going out and doing new things?	1	0
10. Do you feel you have more problems with memory than most people?	1	0
11. Do you think it is wonderful to be alive?	0	1
12. Do you feel pretty worthless the way you are now?	1	0
13. Do you feel full of energy?	0	1
14. Do you feel that your situation is hopeless?	1	0
15. Do you think that most people are better off than you are?	1	0

2.3.2 Imaging Variables

Imaging Technique. T2 fluid attenuation inversion recovery (FLAIR) is an MRI technique in which the pulse sequence parameters are designed to null signal from the cerebrovascular fluid (CSF) and allow for visualization of subtle abnormalities in white matter. In other words, the CSF appears dark, while subtle abnormalities in the brain tissues such as demyelination, gliosis, edema, can be easily seen as bright regions.

White matter hyperintensities (WMH) can be seen on T2 FLAIR brain MRI. Image-acquisition and data-collection protocols vary by ADC. Each ADC submits compressed files of the MRIs in DICOM format to NACC.

Processing. Total volume of T2 FLAIR WMH was calculated by the Imaging of Dementia and Aging (IDeA) Lab at the University of California Davis (Director: Charles DeCarli, M.D.). WMH volumes (in cm^3) were quantified based on the WMH estimation protocol from the Alzheimer's Disease Neuroimaging Initiative-II (ADNI-II). The complete protocol can be found at https://www.alz.washington.edu/WEB/adni_proto.pdf. In addition, Alosco et al. (2018) provides a full detailed description of the WMH estimation methods from the protocol. In brief, the FLAIR is transformed to the T1 image using linear image registration (FLIRT from the FSL toolbox). Inhomogeneity correction of the co-registered FLAIR and T1 is performed using a histogram normalization method. The T1 scan is aligned to a common template atlas and WMH are estimated using a Bayesian probability structure with semi-automatic detection of WMH followed by manual editing. Likelihood estimates of the native image are calculated and all segmentation is performed in standard space to generate probability likelihood values of WMH at each white matter voxel. A threshold of 3.5 standard deviations above the mean is applied to the probabilities to result in a binary WMH mask. The segmented WMH are transformed to native space and summary volume of WMH (in cm^3) is calculated. Gray and white matter are also segmented using an Expectation-Maximization algorithm. A total brain volume composite was calculated as the total sum of gray and white matter segmentations in the brain. Right, left and total frontal and temporal lobe volumes composites were also calculated.

2.4 Statistical Data Analysis

Missing data were identified and properly coded. Descriptive statistics (e.g., mean, standard deviation, skewness) were conducted to examine normal distribution. Boxplots were reviewed to visualize outliers. Appropriate data transformation was applied to the data.

2.4.1 Aim 1: Symptom Profiles of Late-Onset Depression using the GDS-15

To identify symptom profiles of depression using the GDS-15, two structural equation modeling techniques were used: confirmatory factor analysis (CFA) and latent class analysis (LCA). Both the CFA and LCA were performed using Version 8.4 of the Mplus statistical package (Muthén & Muthén, 2019). To ensure optimal LCA model estimation (Wurpts, 2012; Wurpts & Geiser, 2014), all eligible participants in the dataset were used for these analyses (*N*=1192).

Confirmatory Factor Analysis. A CFA was conducted to evaluate the proposed three-factor structure of the GDS-15 consisting of Depressed Mood, (Lack of) Positive Affect and Motivation/Withdrawal factors. The CFA is a variable-centered, theory-driven approach that explicitly tests *a priori* defined relationships between observed variables (e.g., ratings on the GDS-15) and latent factors. Given the categorical data, the weighted least square with mean and variance adjusted (WLSMV) was used for estimation (Li, 2016). WLSMV handles missing data using pairwise deletion (Asparouhov & Muthén, 2010).

A combination of fit indices was used to examine the fit of the 3-factor model. The chi-square value was used to evaluate overall model fit as it assesses the magnitude of discrepancy between observed and predicted covariance matrices (Newsom, 2012). A non-significant chi-square test indicates perfect model fit. One

disadvantage of using this value is that it is sensitive to sample size. In large samples (>1000) the chi-square may falsely reject an adequate model. Relative fit indices were also used to evaluate model fit including the comparative fit index (CFI), the Tucker Lewis index (TLI), the root mean error of approximation (RMSEA), and standardized root mean square residual (SRMR). Hu and Bentler (1999) suggested that the following cutoffs indicate acceptable fit: RMSEA values less than .08, TLI and CFI values greater than .95, and SRMR values less than .08. Yu (2002) reported that these cutoff values were also appropriate for categorical data. Following the assessment of model fit, parameter estimates were interpreted. Factor loadings that were significant (p<.05) and greater than 0.4 were considered acceptable.

Latent Class Analysis. An LCA was performed to identify and describe latent classes in this sample. The LCA is a person-centered modeling technique that allows individuals who share similar characteristics to be clustered in latent classes that are assumed to be mutually exclusive and exhaustive (Lanza & Rhoades, 2013). LCA uses an iterative process to fit several models to the data, each with an increasing number of classes (e.g., 2-, 3-, and 4-class solutions). Comparisons between the models are used to determine which model best fits the data. LCA calculates probabilities based on responses to each item and how similar or different the responses are to each other. The LCA also assigns participants to one of the identified latent classes (i.e., most likely class membership) based on the conditional probability that the participant's observed response pattern on the items aligns with the latent class. Beginning with a two-class model, an increasingly larger number of class models were estimated. Class enumeration was determined using five indicators of model fit (Logan & Pentimonti,

2016; Nylund, Asparouhov, & Muthén, 2007): Lo–Mendell–Rubin likelihood ratio test (LMR), Akaike information criterion (AIC), Bayesian information criterion (BIC), -2 log likelihood (-2LL) value, and model entropy. The Lo–Mendell–Rubin likelihood ratio test (LMR) compares the improvement in fit with each iterative model (i.e., comparing k-1 and the k class models). LMR generates a *p* value that indicates a statistically significant improvement in model fit. The AIC/BIC reflects how well the model predicts the data, with lower values indicating better model fit. -2 log likelihood (-2LL) value is a chi-squared comparison test between models, with reductions in -2LL suggest better fit. Model entropy indicates how much differentiation there is between the different classes in the model, with values closer to 1 indicating greater classification accuracy. Clark & Muthén (2009) suggests that entropy values of 0.80 is high, 0.60 is medium and 0.40 is low. Asparouhov and Muthen (2014) further suggested that entropy ≤0.60 is poor. Multiple sets of randomly generated starting values were used to avoid converging on a local solution.

It is common that the fit indices do not converge on one single model, rather fit indices may support one or two candidate models. As such, model selection was based on a balance of statistical markers of model fit and model interpretability. For model selection, the BIC and LMR where first used to narrow down the number of models based on Nylund et al. (2007) recommendations. The models were then explored visually to examine the item probability plot by latent classes in order to determine theoretically aligned differences among the classes. Model entropy and relative sizes of the classes were then explored to avoid an over-extracted and unstable class solution. A well-accepted rule is that no latent class should contain less than 5% of individuals in the sample (Logan & Pentimonti, 2016). The most parsimonious model was selected,

and participants were assigned to their most likely class membership. This class membership (i.e. group membership) data was extracted for ANCOVA analyses in SPSS.

2.4.2 Aim 2: Group Differences in WMH Volume

To address the second aim of the study, an ANCOVA was conducted to examine differences in WMH volumes by latent class membership. A subsample of participants with calculated WMH volumes were included in these analyses (n = 423). Potential covariates were examined prior to inclusion in the model. Specifically, demographic variables (age, sex, race, education level) that have previously been found to have a relationship with WMH were examined. In addition, total brain volume was included as a covariate to adjust for individual differences in brain volume that may influence the volume of WMH. Class membership was the independent variable and WMH volume was the dependent variable.

The same analytic approach was used for exploratory analyses using frontal and temporal brain volumes as dependent variables instead of WMH volumes. In these exploratory ANCOVA analyses, total intracranial volume (ICV) was included as a covariate to control for the impact of head size on brain volume.

ANCOVA analyses were conducted in SPSS and values of $p < .05$ were considered statistically significant. Bias-corrected and accelerated bootstrapped confidence intervals using 10,000 bootstrap samples were also obtained.

2.4.3 Aim 3: Subthreshold Depressive Symptoms & WMH Volume

Analyses for Aim 3 paralleled those for Aim 2; however, the sample was stratified by clinical diagnosis (depressed versus non-depressed). Participants were included in the

subthreshold depression group if they 1) scored between one and the clinical cutoff of 5 on the GDS-15 and 2) did not endorse current depression in semi-structured interview.

2.4.4 Symptom Dimensions of Late-Onset Depression & Structural Brain Markers

Given the use of symptom dimensions of depression in the literature, regression analyses were also conducted to examine the relationship between symptom dimensions of depression, using the GDS-15, and structural brain markers (i.e., WMH, frontal and temporal lobe volumes). The CFA validated three-factor structure of the GDS-15 resulting in depressed mood, lack of positive affect and motivation/withdrawal subscales were used in these analyses. Total scores for each subscale were calculated and used as continuous predictors in the regression analyses, while each structural brain marker was the dependent variable. Each regression model included age, sex, race and education level as covariates. Total brain volume and total intracranial volume were also included in the models predicting WMH and cortical volumes, respectively.

3 RESULTS

A final sample of 1,192 participants were retained. The full sample was used for the CFA and LCA, while a subsample of participants with calculated WMH volumes were used for the ANCOVA (n = 423). Descriptive characteristics of the full sample are presented in Table 3.1 (see Table 3.4 for descriptive characteristics of the subsample).

3.1 Data Cleaning

Upon inspection, the distribution of the WMH volume variable was positively skewed (SkewnessWMH = 2.42, SE = .119). Log transformation was applied which normalized the distribution (SkewnessWMH = .238, SE = .119; SkewnessGDS = .860, SE = .119). No outliers were present.

3.2 Aim 1: Symptom Profiles of Late-Onset Depression using the GDS-15

Confirmatory Factor Analysis

The hypothesized three-factor CFA with the proposed constructs (Depressed mood, (Lack of-) Positive affect, Motivation/Withdrawal) was tested. This measurement model exhibited good fit to the data, $\chi^2(74) = 113.444$, $p < .05$, CFI = .980, TLI = .976, RMSEA = .021 (90% CI: .013-.029) and SRMR = .076. All indicators significantly loaded onto their respective factors above .04, at the $p < 0.001$ level. The three factors were all highly correlated ($p < .001$), with correlations above .80 (Figure 3.1). The large correlation indicated that the factors overlap greatly. A post-hoc one-factor model was therefore fit to the data to examine the overall fit relative to the three-factor model, $\chi^2(77) = 136.112$, $p < .001$, CFI = .970, TLI = .965, RMSEA = .025 (90% CI: .018-.032) and SRMR = .086. The fit indices were similar between the one- and three-factor model, except for SRMR. The combination of a more significant chi-square test and SRMR value greater than .80 suggested that the one-factor model was a less adequate fit for the data. These results provide some evidence that despite the high correlation between subscales on the GDS-15 in this sample, the three-factor model was a better fit than the one-factor model.

Table 3.1 *Descriptive characteristics for the full sample (N = 1,192)*

Variable	Mean ± SD (Range) or *n* (%)
Age	75.2 ± 6.93 (65-100)
Education	15.7 ± 3.19 (0-25)
Sex (N,%)	
Male	453 (38%)
Female	739 (62%)
Race (N,%)	
White	995 (83.5%)
Black	123 (10.3%)
Asian	33 (2.8%)
American Indian/Alaska Native	7 (0.6%)
Native Hawaiian/Pacific Islander	1 (0.1%)
Multiracial	30 (2.5%)
Mood (N,%)	
Clinical Depression*	18 (1.5%)
Anxiety⁺	115 (9.6%)
GDS-15 Total	1.00 ± 1.63 (0-12)
GDS-15 Score (N,%)	
Normal range (GDS<5)	1,145 (96%)
Clinical range (GDS ≥5)	47 (4%)

Note. *Clinician Diagnosis, ⁺Participant Report

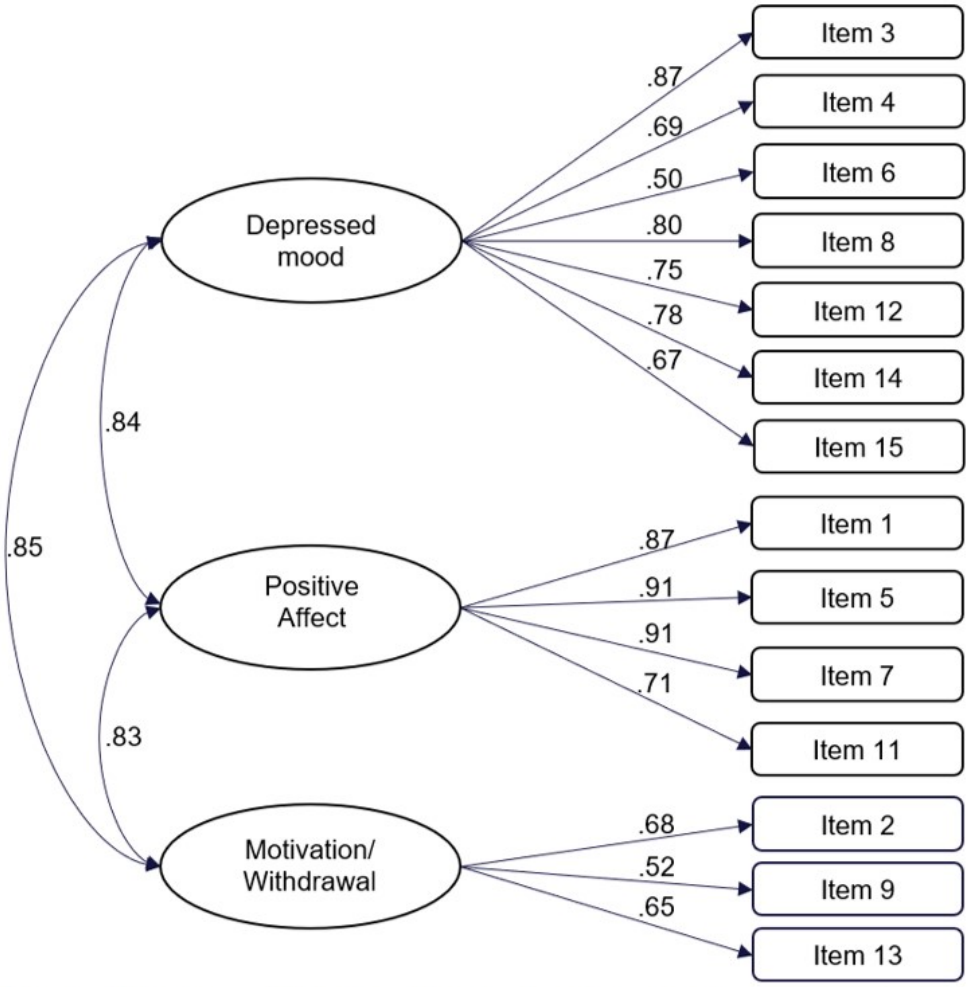

Figure 3.1 Three-factor model: Confirmatory factor analysis for the GDS-15. Note. Standardized estimates are shown.

Latent Class Analysis

The appropriate number of latent classes was identified by estimating and comparing a series of models with an increasing number of classes. In all LCA models, the best log likelihood value was replicated for multiple starting values suggestive of good model stability. Model fit indices were extracted and presented in Table 3.2. The two-class LCA model was a significant fit to the data (p <.001). The three-class LCA model was not a significant improvement over the two-class model (LMR, p= .089).

Relatively, the four-class LCA model demonstrated model improvement over the three-class model (LMR, p <.05). The five-class LCA model was not significant (LMR, p =.628) and model estimation was discontinued. The BIC value suggested that the two-class model was a better fit relative to the four-class model. The entropy values for both two- and four-class models were high, suggesting that both model solutions had good classification accuracy. When graphed, the two-class model demonstrated theoretically meaningful latent classes while the four-class model showed overlaps between classes and no clear interpretation was able to be determined. Additionally, the two-class model had more than 5% of the sample in each class, unlike the four-class model, which resulted in two classes with 2% and 3% of the sample in two respective classes.

Table 3.2 *Model fit indices for latent class models.*

Number of groups	-2LL	Free parameters	AIC	BIC	Entropy	LMR p value
2	-3544.187	29	6304.490	6451.908	.902	.000
3	-3123.245	44	6231.782	6455.451	.661	.089
4	-3071.891	59	6184.212	6484.132	.734	.041
5	-3033.106	74	6166.356	6542.527	.753	.628

Note. -2LL =2 log likelihood, LMR=Lo–Mendell–Rubin likelihood ratio test

The two-class model was therefore selected as the more parsimonious model. The interpretation of the latent classes was based on conditional probabilities, with values closer to 1 representing a higher probability of endorsing the item. There was a striking difference between both classes (Figure 3.2). Individuals in Class 1 (10% of the sample) had a higher probability of endorsing all depressive symptoms with greater probability of endorsing lack of positive affect and motivation/withdrawal symptoms. In contrast, Class 2 (90% of sample) had low to no probability of endorsing the depressed mood and lack of positive affect symptoms and greater probability of endorsing all

motivation/withdrawal symptoms. As such, Class 1 was labeled General Depression and Class 2 was labeled Motivation/Withdrawal. Of note, despite the relatively greater endorsement of motivation/withdrawal symptoms in Class 2 (i.e., Motivation/Withdrawal), Class 1 (i.e., General Depression) demonstrated a higher probability of these symptoms as well, consistent with the greater overall probability of depressive symptom endorsement in this class.

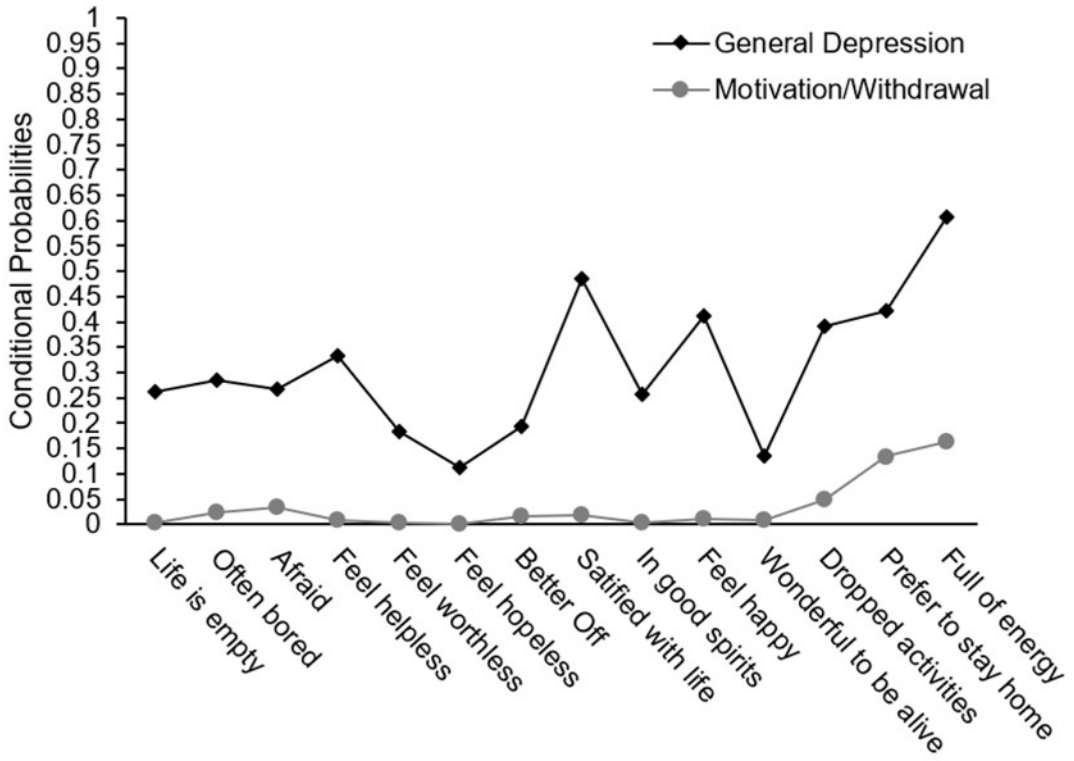

Figure 3.2 Conditional probabilities of a two-factor solution of the GDS-15.

In the model, the Motivation/Withdrawal class, which contained a majority of the sample (90%), appeared to consist of low to no probability of depression symptoms. Considering the demographics of the overall sample (e.g., generally clinically healthy community-dwelling individuals) in the context of the probability pattern in the model, it was postulated that the sample may contain a true asymptomatic class which may be subsumed into the Motivation/Withdrawal class. It would be theoretically and clinically

meaningful to determine whether the Motivation/Withdrawal latent class holds true, even after estimating an asymptomatic class. As such, the LCA was re-run with a pre-specified zero class to consist of individuals with zero probability of endorsing any of the depression symptoms. In order words, model restrictions were placed on one class in a constrained LCA in which the threshold was set to ensure that the conditional response probabilities on all symptoms was constrained to zero, using deterministic model restrictions (Finch & Bronk, 2011; McCutcheon, 2002). Model fit indices are presented in Table 3.3.

Table 3.3 *Fit Indices for constrained LCA models*

Number of groups	-2LL	Free parameters	AIC	BIC	Entropy	LMR *p* value
2	-3544.187	15	6590.903	6667.154	.741	.000
3	-3123.245	30	6214.437	6366.939	.665	.0001
4	-3071.891	45	6169.503	6398.255	.717	.0295
5	-3033.106	60	6148.544	6453.548	.748	.144

Note. -2LL =2 log likelihood, LMR=Lo–Mendell–Rubin likelihood ratio test

Four LCA models were estimated, with the number of classes ranging from two to five. All constrained models except for the five-class model (LMR, $p = 0.144$) were significant. The BIC values favored the three-class model relative to the two- and four-class models. Visually, the constrained three-class model (Figure 3.3) resembled the previously described unconstrained two-class model (Figure 3.2), except for the pre-specified zero-class (Asymptomatic) latent class. Both model solutions yielded a class structure consisting of General Depression and Motivation/Withdrawal classes. Furthermore, the AIC and BIC values suggested that the constrained three-class model (AIC = 6214.437, BIC = 6366.939) was a relatively better fit to the data than the unconstrained two-class model previously estimated (AIC = 6304.490, BIC = 6451.908).

The constrained three-class model had an entropy value of 0.665, suggesting that the classification accuracy for the constrained model was less strong than that for the unconstrained two-class model, described above (entropy = .902). Examining the classification probabilities of the constrained three-class model, the reduced classification was localized to the Motivation/Withdrawal class. Individuals assigned to the Motivation/Withdrawal class had a classification probability of 69.3%, but also had an approximately 29.5% chance of belonging in the Asymptomatic class. Although, the entropy value was reduced, it fell within the medium range (>.60) and the classes were considered to be adequately separated. Overall, assuming a true zero-class (Asymptomatic; *n* = 701) once again resulted in a model solution including Motivation/Withdrawal (*n* = 417) and General Depression (*n* = 74) classes, and this constrained model solution was a better fit to the data. Using the constrained three-factor model, the most likely class membership was assigned for each participant based on their pattern of responses on each item. These class membership designations were used in further analyses in Aim 2 & 3 and will henceforth be referred to as the General Depression, Motivation/Withdrawal and Asymptomatic groups.

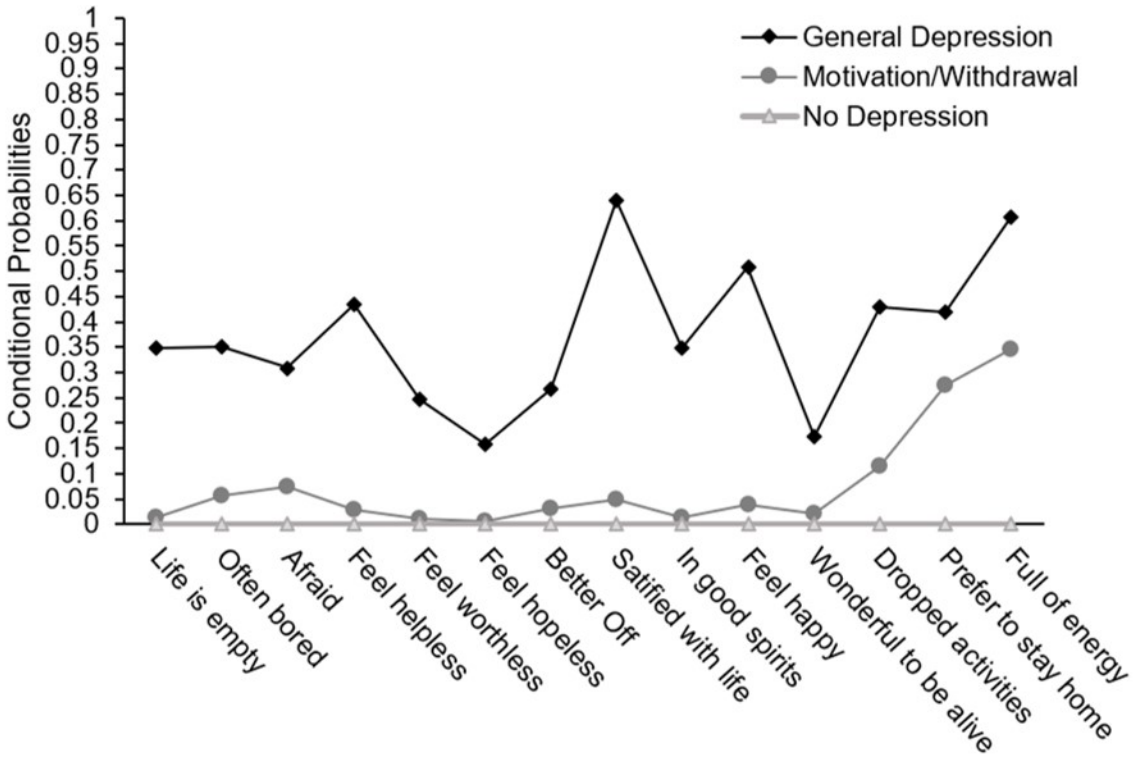

Figure 3.3 Conditional probabilities of the constrained three-factor model

3.3 Aim 2: Group Differences in WMH Volume

As described above, a subsample of participants with calculated volumes of WMH were included in the ANCOVA. Descriptive statistics for this subsample are presented in Table 3.4. Participants across groups had a mean age of 77-78 years, were predominantly female, white and had on average more than 12 years of education. The General Depression group endorsed the highest level of depressive symptoms on the GDS-15 on average, with 68% of individuals in the General Depression group falling above clinical cutoffs on the GDS-15. All participants in the Motivation/Withdrawal and Asymptomatic groups fell in the subthreshold range of the GDS-15. 47% of participants in the General Depression group endorsed subjective anxiety, relative to 7% and 6% in the Motivation/Withdrawal and Asymptomatic groups, respectively.

Table 3.4 *Descriptive Statistics for the ANCOVA sample*

Variable	Total Sample	General Depression	Motivation/ Withdrawal	No Depression
		Mean ± SD or *n* (%)		
N	423	38	161	224
Age	77.75±7.23	77.58±6.83	78.7±7.05	77.09±7.47
Years of Education	14.65±3.69	13.11±4.57	14.54±57	14.99±3.56
Sex (N,%)				
Male	166 (39%)	13 (34%)	74 (46%)	79 (35%)
Female	257 (61%)	25 (66%)	87 (54%)	145 (65%)
Race (N,%)				
White	320 (76%)	30 (79%)	121(75%)	169 (75%)
WMH volume (cm^3)	8.90±11.42	8.33±1.56	11.08±0.1.02	7.43±0.69
Natural log of WMH	0.77±0.43 (0.01-1.87)	0.81±0.36 (0.14-1.67)	0.86±0.45 (0.03-1.84	0.71±0.42 (.01-1.87)
Mood (N,%)				
Clinical Depression*	3 (0.7%)	2 (5%)	1 (0.6%)	0
Anxiety⁺	43 (10.2%)	18(47%)	12 (7%)	13(6%)
GDS-15 Total	1.24±1.94	6.13±2.35	1.75±0.82	0.05±0.23
Normal range (GDS<5)	397 (93.9%)	12(32%)	161(100%)	224(100%)
Clinical range (GDS≥5)	26 (6.1%)	26 (68%)	0	0
GDS-15 Subscales				
Depressed Mood	0.32±0.8 (0-5)	2.30±1.29 (0-5)	0.30±0.47 (0-2)	0
Positive Affect	0.23±0.66 (0-4)	1.79±1.23 (0-4)	0.15±0.37 (0-2)	0
Motivation/Withdrawal	0.55±0.8 (0-3)	1.65±0.97 (0-3)	1.06±0.70 (0-3)	0

Note. *Clinician Diagnosis ⁺Participant report on the Neuropsychiatric Inventory Questionnaire (NPI-Q)

Pearson bivariate correlations, chi-square tests and ANOVAs were used to determine which potential confounding demographic variables (i.e., age, sex, education, race/ethnicity) met criteria to be included in the ANCOVA. To be included in the ANCOVA, potential covariates were independent of the treatment effect (i.e., group membership) or were related to the outcome variable (WMH volume), and did not contribute to the violation of the homogeneity of regression slopes assumption. In the current sample, education level was significantly different between the groups ($p<.05$), while the other demographic variables did not significantly differ across groups. Age was significantly related to WMH volume ($r = .38$, $p<.001$), while the other demographic variables were not significantly related. Accordingly, age and education level were included as demographic covariates in the ANCOVA. Specific to analysis with WMH volume, total brain volume was included as a covariate. Data was checked for violations of the assumptions for ANCOVA. No outliers were identified. Assumptions of normality, homogeneity of variance, and homogeneity of regression slopes were all satisfactory.

After controlling for age, education, and total brain volume, there was a significant effect of group membership on WMH volume, $F(2,416) = 4.22$, $p<.05$, with a small effect size ($\eta_p^2=.02$). Post hoc comparisons were conducted to evaluate pairwise differences among the adjusted means, using the Bonferroni procedure (Table 3.5). Results showed that individuals in the Motivation/Withdrawal group had significantly higher WMH volumes relative to those in the Asymptomatic group, even after controlling for the effect of age and education (Figure 3.4). Although the Motivation/Withdrawal group had a higher WMH volume compared to the General Depression group, the adjusted mean difference was not statistically significant. Similarly, the General Depression and Asymptomatic groups did not significantly differ. These findings

remained unchanged when the presence of anxiety was included as a covariate, $F(2,386) = 4.78$, $p<.05$, $\eta p^2 = .02$.

Table 3.5 WMH Volume m*ean difference by group membership (n = 423*)

Comparison	Mean Difference	Standard Error	BCa 95% CI
WMH Volume⁺			
General Depression vs. Motivation/Withdrawal	-0.03	0.07	-0.16, 0.10
General Depression vs. Asymptomatic	0.09	0.06	-0.03, 0.21
Motivation/Withdrawal vs. Asymptomatic	0.12*	0.04	0.03, 0.21
Frontal Lobe Volume			
General Depression vs. Motivation/Withdrawal	1.85	2.061	-3.10, 6.81
General Depression vs. Asymptomatic	1.18	2.008	-3.65, 6.00
Motivation/Withdrawal vs. Asymptomatic	-0.68	0.186	-3.53, 2.17
Temporal Lobe Volume			
General Depression vs. Motivation/Withdrawal	0.01	1.21	-2.91, 2.91
General Depression vs. Asymptomatic	0.64	1.18	-2.20, 3.47
Motivation/Withdrawal vs. Asymptomatic	0.64	0.70	-1.04, 2.31

Note. Comparisons are based on ANCOVA adjusted means for covariates. ⁺Natural log of WMH volume. **p*<.05, where p-values are adjusted using the Bonferroni method. BCa 95% CI= bias-corrected and accelerated 95% confidence interval.

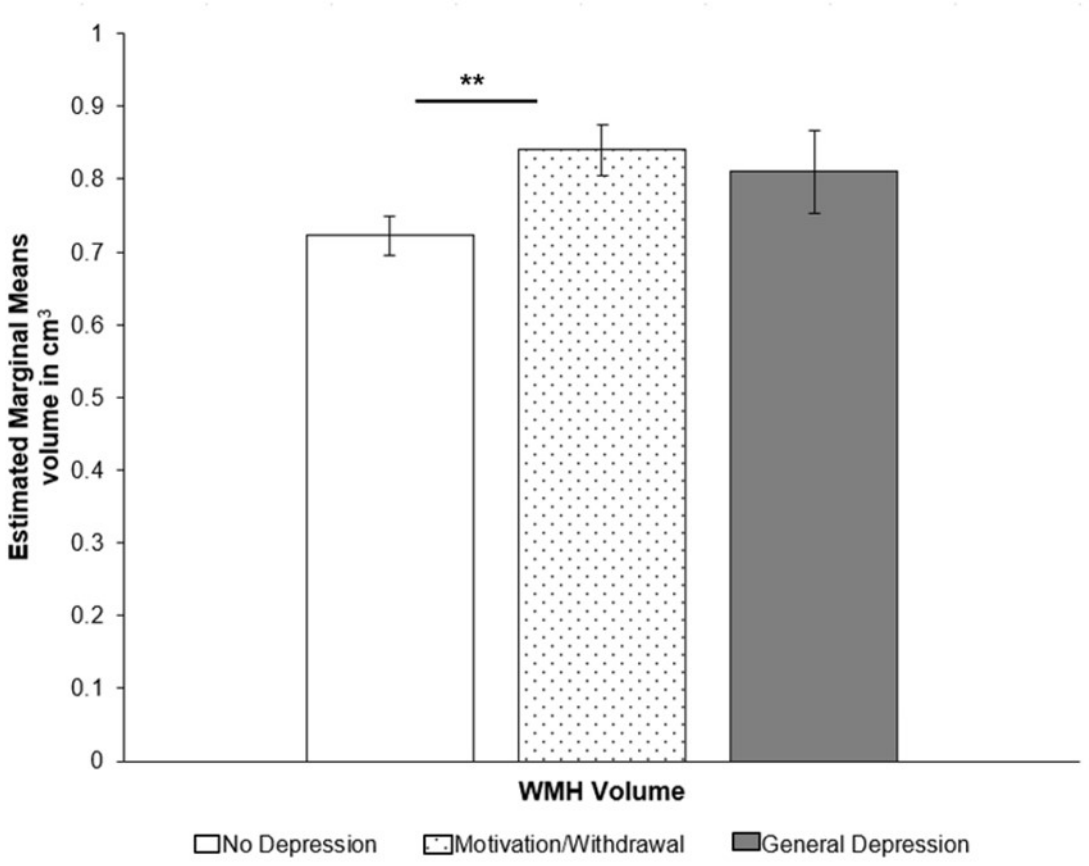

Figure 3.4 Covariate-adjusted WMH volume means by class membership. Error bars represent bootstrapped standard error. WMH=white matter hyperintensities. **Indicates significant difference at $p<.01$

3.3.1 Exploratory Analyses: *Frontal and Temporal Brain Volumes*

Two separate ANCOVA models were conducted using total frontal and temporal brain volumes as dependent variables (Table 3.5). Group membership (i.e., General Depression, Motivation/Withdrawal, Asymptomatic) remained the independent variable. Potential covariate analyses revealed that age, sex and education level were all significantly related to frontal and temporal brain volumes. Total intracranial volume was also included in each model to control for the effect of head size on brain volume.

Total frontal lobe brain volume. There were no violations of the assumptions for the ANCOVA examining the difference in total frontal brain volume by group

membership. Results showed no significant effect of class membership on frontal brain volume, $F(2,415) = 0.45$, $p = .641$.

Total temporal brain volume. For the ANCOVA model examining the effect of group membership on total temporal brain volume, the assumption of homogeneity of regression slopes was violated by the sex covariate; as such sex was not used as a covariate in this ANCOVA model. The assumption of normality was also violated, specifically in the General Depression group. As such, robust methods (i.e., bootstrapping) were used to examine group differences (Fields, 2010). Results revealed no significant differences in total temporal brain volume by group membership (Table 3.5).

3.4 Aim 3: Subthreshold Depressive Symptoms & WMH Volume

Follow-up stratified ANCOVA models were conducted to examine the impact of clinical diagnosis on the relationship between WMH volumes and group membership (Table 3.6).

Subthreshold depression. A total of 170 participants were included in this analysis including 159 participants in the Motivation/Withdrawal group, and 11 participants in the General Depression group. No participants in the Asymptomatic group were included in this analysis, as they endorsed less than a score of 1 on the GDS-15. Similarly, while WMH volume was greater in Motivation/Withdrawal group ($M_{Adjusted} = 0.86$, SE = 0.36) compared to General Depression ($M_{Adjusted} = 0.80$, SE = 0.12), there was no significant difference, $F(1,164) = .181$, $p = .67$. There were also no significant differences in frontal ($F(1,163) = .55$, $p = .46$) and temporal ($F(1,163) = 2.75$, $p = .10$) volumes across the two symptom profiles.

Clinical depression. Only 3 of the 432 participants had a diagnosis of clinical depression. When stratifying by GDS-15 clinical cut-off score, 26 participants met criteria for depression (GDS-15 ≥5) and were all in the General Depression group. As such, the ANCOVA was not performed.

Table 3.6 *Mean difference between General Depression and Motivation/Withdrawal in subthreshold sample (n = 170)*

Volume	Mean Difference	Standard Error	BCa 95% CI
WMH	-0.06	0.12	-0.20, .288
Frontal Lobe	2.52	3.68	-4.41, 4.93
Temporal Lobe	-3.51	2.65	-8.87, 1.80

Note. Comparisons are based on ANCOVA adjusted means for covariates. ⁺Natural log of WMH volume. **p*<.05, where p-values are adjusted using the Bonferroni method. BCa 95% CI= bias-corrected and accelerated 95% confidence interval.

3.5 Symptom Dimensions of Depression & Structural Brain Markers

Results of regression analyses are presented in Table 3.7. There was a significant association between WMH volume and scores on the depressed mood (*β = .09*) and motivation/withdrawal (*β = .102*) subscales, even after controlling for age, sex, education level, race and total brain volume. Frontal lobe volumes were not significantly related to any of the subscale scores. Temporal lobe volumes were not significantly related to depressed mood and motivation/withdrawal subscale scores, but scores on the positive affect subscale were marginally related. In a subset of individuals with subthreshold depressive symptoms (*n* = 170), WMH volume was not significantly associated with any subscale scores. Similarly, frontal and temporal lobe volumes were not significantly related with scores on the subscales; although, motivation/withdrawal subscale scores were marginally related to left frontal lobe volume.

Table 3.7 *Results of Regression Analyses*

	Full Sample			*Subthreshold Sample*		
Variable	B	SE	*p* value	B	SE	*p* value
WMH Volume						
Depressed Mood	0.05	0.03	**.040**	.06	.05	.235
Positive Affect	0.03	0.03	.291	-.03	.07	.638
Motivation/Withdrawal	0.06	0.02	**.025**	-.00	.05	.987
Frontal Lobe						
Total						
Depressed Mood	-0.14	0.71	.840	-0.45	1.38	.746
Positive Affect	0.59	0.84	.482	*-0.28*	1.70	*.871*
Motivation/Withdrawal	0.31	0.70	.660	1.39	1.21	.255
Right						
Depressed Mood	-0.02	0.34	.962	-0.04	0.67	.949
Positive Affect	0.38	0.40	.340	0.22	0.83	.791
Motivation/Withdrawal	-0.20	0.34	.953	0.16	0.59	.788
Left						
Depressed Mood	-0.11	0.38	.766	-0.35	0.76	.647
Positive Affect	0.20	0.45	.668	*-0.51*	*0.93*	*.589*
Motivation/Withdrawal	0.32	0.38	.396	1.22	0.66	*.067*
Temporal Lobe						
Total						
Depressed Mood	0.08	0.42	.845	-0.38	0.86	.660
Positive Affect	0.93	0.49	*.059*	-0.16	1.06	.880
Motivation/Withdrawal	0.64	0.41	.122	0.79	0.76	.301
Right						
Depressed Mood	0.03	0.22	.886	-0.03	0.46	.949
Positive Affect	0.44	0.26	*.099*	0.13	0.57	.825
Motivation/Withdrawal	0.29	0.22	.194	0.25	0.40	.533
Left						
Depressed Mood	0.06	0.22	.782	-0.33	0.46	.483
Positive Affect	0.50	0.26	*.059*	-0.29	0.57	.618
Motivation/Withdrawal	0.35	0.22	.112	0.51	0.41	.210

4 DISCUSSION

The current study was designed to 1) identify symptom profiles of late-onset depression, 2) investigate differences in white matter hyperintensities (WMH) between identified symptom profiles of late-onset depression, and 3) examine whether the relationship between WMH and symptom profiles of late-onset depression was similar in subthreshold levels of depression.

4.1 Symptom-Based Approach to Late-Onset Depression

Results from Aim 1 provide support for the prediction that qualitatively different symptom profiles would emerge in older adults with depression. Latent class analysis successfully identified a motivation/withdrawal symptom profile, in addition to a symptom profile characterized by broad endorsement of all depression symptoms with a greater probability of endorsing lack of positive affect and motivation/withdrawal symptoms of depression. These findings are consistent with three studies that have also found qualitatively distinct symptom profiles of depression in older adults (Lee et al., 2012; Lohman et al., 2014; Mora et al., 2012). In contrast to three latent class analysis studies conducted by Hybels and colleagues (2011; 2009; 2013), results from the current study were not simply separated by depression severity, but also by qualitative differences. Discrepant findings may be explained by differences in participant characteristics as the sample in Hybels et al. (2011; 2009) consisted of older adults with clinical depression across in-patient and out-patient settings, while Hybels et al. (2013) included community-dwelling older adults, who were demographically dissimilar from the current study (predominantly non-White, less than 12 years of education, some with cognitive impairment). In the current study, while the symptom profiles did differ in

severity (e.g., General Depression symptom profile had a greater probability of endorsing all symptoms relative to the Motivation/Withdrawal symptom profile), the qualitative differences were more distinctive.

Consistent with hypotheses, the current study identified a symptom profile with a clear symptomatic dimension consisting of motivation and withdrawal symptoms. However, purely depressed mood or lack of positive affect symptom profiles were not identified as predicted. Our findings are most consistent with Lohman et al (2014) who reported a distinct “somatic depression” symptom profile, in addition to three other symptom profiles separated by severity. The “somatic depression” symptom profile was based on a higher probability of endorsing three items on the CES-D 8 that are similar in kind to the motivation items on the GDS-15 (i.e., “I could not get “going” and “I felt that everything I did was an effort”), as well as a third item assessing a somatic symptom (i.e., sleep difficulties). While the GDS-15 purposefully omits somatic symptoms that may be attributed to medical illness (Balsamo et al., 2018), it is possible that the items assessing motivation or withdrawal symptoms still reflect somatic burden. Endorsement of items purported to capture motivation and withdrawal symptoms on the GDS-15 (“Have you dropped many of your activities and interests?”, “Do you prefer to stay home, rather than going out and doing new things?”, and “Do you feel full of energy?”) may truly reflect changes in depressive symptomatology (either motivation/withdrawal symptoms or somatic depression) or may be an artifact of somatic illness. For example, an individual may have dropped their activities because physical limitations preclude their participation or may experience fatigue due to a comorbid medical condition. Unfortunately, somatic and physical changes were not

consistently measured in the NACC database and these potentially confounding contributors could not be systematically accounted for.

Two factor analytic studies provide some evidence that the motivation and withdrawal symptoms measured on the GDS-15 may not overlap with somatic symptoms. Namely, in a sample of community-dwelling older adults with major depression, results consistent across both studies did not yield a factor consisting of motivation or withdrawal symptom items on the GDS-30 and somatic symptoms on the 15-item Patient Health Questionnaire, a somatic symptom subscale derived from the full Patient Health Questionnaire (Grover, Sahoo, Chakrabarti, & Avasthi, 2019; Mehra, Grover, Chakrabarti, & Avasthi, 2017). In other words, the items measuring motivation and withdrawal depressive symptoms on the GDS-30 do not also tap into a somatic construct. The same motivation and withdrawal items on the GDS-15 are identical to those on the GDS-30, and these factor analytic studies provide some support that the motivation and withdrawal symptom profile is characterized by changes in these aspects of depression rather than somatic depression.

Findings from Aim 1 underscore the importance of a symptom-level approach to depression in older adults. The majority of individuals with the general depression symptom profile met clinical cutoffs on the GDS-15 (68%), while none of the individuals with the motivation/withdrawal symptom profile fell within the clinical range. These individuals endorsed subthreshold depressive symptoms, and were statistically distinct from non-depressed older adults. In addition, 32% of individuals with the general depression symptom profile also fell below clinical cutoffs on the GDS-15, which further supports that idea that subthreshold levels of depressive symptoms are important to

explore. Clinically, only a small number of individuals would fall in clinical range on this commonly used symptom inventory (9% of full sample), while others with notable depression symptoms may be missed. The under-recognition and under-treatment of depressive symptoms in older adults is a widely acknowledged phenomena (Reynolds, Alexopoulos, Katz, & Lebowitz, 2001). These results highlight how symptom-level approaches to depression might improve the identification of depressive symptoms in older adults.

In addition to latent class analysis, the current study also used confirmatory factor analysis to examine symptom patterns of depression in older adults. Results validate the depressed mood, lack of positive affect and motivation/withdrawal symptom dimensions on the GDS-15 consistent with Mitchel et al. (1993) findings. High inter-factor correlations suggest that these factors on the GDS-15 are largely similar, and raise concern that they may not represent clearly distinct constructs that can serve as meaningful subscales. One unpublished study, presented at the International Neuropsychological Society conference, using exploratory and confirmatory factor analyses, found that a one-factor structure fit the GDS-15 in adults aged 16-94 years (M = 57.44, SD = 19.97) (Launeanu & Hubley, 2012). In contrast, results from the current study, which only included older adults, suggests that a three-factor structure is a better fit, relative to the one-factor structure. Our findings suggest that the total scores from the three subscales, while highly correlated, are likely to present a more nuanced understanding and interpretation of depressive symptoms in older adults.

The current study is the first, to the best of our knowledge, to identify symptom profiles of depression in older adults without a history of depression in earlier life. The

emergence of the motivation/withdrawal symptom profile adds to the literature showing that “depression without sadness” occurs in older adults (Gallo et al., 1999; Gallo et al., 1997). Even within the General Depression symptom profile, depressed mood symptoms are relatively less likely than are positive affect and motivation/withdrawal symptoms. No symptom profile characterized by prominent depressed mood emerged, despite depressed mood being considered a depression hallmark in our current diagnostic criteria and a phenotypic benchmark of depression used by both health professionals and patients alike (Gum et al., 2009).

One important consideration is whether this depression presentation in older adults represents a cohort effect or is truly a distinct depression experience in later life. Earlier studies have suggested that older adults may be reticent to endorse depression relative to younger adults (Lyness et al., 1995) based on societal and cultural norms around mental health, and are more likely to attribute symptoms of depression to a medical or physical condition (Knäuper & Wittchen, 1994). Birth cohort analysis studies suggest variability in depression symptom endorsement in older adults across birth cohorts as a function of time, theorized to be associated with decreased functional impairment over time, changed perspective on life post-World War II, and improved health behaviors (Keyes et al., 2014; Sullivan et al., 2020; Tampubolon & Maharani, 2017). Sullivan et al. (2020) found that older adults born closer to the start of the 20th century endorsed greater depressed mood, hopelessness and withdrawal depressive symptoms relative to more recent born cohorts (e.g., 1932-1941), even after controlling for the effect of medical morbidity. These findings show variability in symptom endorsement *within* older adults across time. If the depression patterns reported in the

literature were a result of under-reporting due to stigma, one would not necessarily expect greater depressive symptom endorsement in earlier compared to later birth cohorts, given less negative attitudes toward depression over time (in the United States) due to public health efforts to increase knowledge and awareness of depression (Blumner & Marcus, 2009). These cohort studies provide some support of a distinct depression experience in late-life depression, that may not be simply attributed to a cohort effect.

4.2 WMH Difference Across Symptom Profiles of Late-Onset Depression

The presence of white matter changes in late-life depression is well documented. Numerous studies have shown greater WMH in older adults with depression relative to non-depressed older adults (Greenwald et al., 1996; Kirton et al., 2014; O'Brien et al., 2006; Steffens, Bosworth, Provenzale, & MacFall, 2002; Taylor et al., 2005), and individuals with late-onset depression demonstrate greater WMH burden relative to early-onset and non-depressed older adults (Hickie et al., 1995; Salloway et al., 1996; Salo et al., 2019). The current study is the first to examine differences in WMH volume across symptom profiles of depression in older adults without a history depression in earlier life.

Results showed no statistical difference in WMH volume between the General Depression and Motivation/Withdrawal symptom profiles despite distinct symptomatic differences. However, it should be noted that individuals with the Motivation/Withdrawal symptom profile had the highest volume of WMH compared to General Depression and Asymptomatic profiles, consistent with hypothesis. The lack of statistical significance for this difference might be attributable to the fact that both the Motivation/Withdrawal and

the General Depression symptom profiles were characterized by motivation and withdrawal symptoms. The former profile demonstrated a higher probability of endorsing motivation and withdrawal symptoms compared to little-to-no probability of endorsing all other depressive symptoms on the GDS-15. The latter symptom profile consisted of a higher probability of endorsing all depressive symptoms including motivation and withdrawal symptoms. Findings suggest that motivation and withdrawal symptoms may be related to WMH volume even when other depressive symptoms are minimal. In addition, individuals with the Motivation/Withdrawal symptom profile had a statistically higher WMH volume relative to asymptomatic individuals, while the General Depression profile did not, which provides further support that motivation and withdrawal symptoms, in particular, may be linked to WMH in this population, consistent with hypotheses. Interestingly, the initial (unconstrained) LCA clustered individuals in the Motivation/Withdrawal and Asymptomatic latent classes. Constrained LCA was used to separate the asymptomatic class which demonstrated good fit to the data, and now appears to be neurologically different from the Motivation/Withdrawal latent class, providing support for the validity of our approach and solution.

While individuals with the General Depression symptom profile had higher WMH volumes compared to asymptomatic individuals, who had the lowest WMH volumes in the sample, this difference did not reach statistical significance. Given the extensive literature showing that WMH differ between older adults with and without depression, it was expected that WMH volume would also differ between individuals without depressive symptoms and those with the General Depression symptom profile who had the highest depression severity in the sample. Null findings could be attributed simply to

the restricted number of individuals with the General Depression profile relative to the Motivation/Withdrawal and Asymptomatic profiles in group comparison analyses. Alternatively, findings may suggest that other neurobiological factors, in addition to WMH, may contribute in an additive manner to depressive symptoms in individuals with a general depression symptom profile, even in late-onset depression. Given the more prominent positive affect, motivation, and withdrawal symptoms, potential contributory factors may also impact the fronto-striatal circuitry and/or reward circuitry specifically (Heshmati & Russo, 2015). Future studies examining candidate brain regions (e.g. prefrontal regions, nucleus accumbens), and pathways (e.g., mesolimbic dopamine pathways) may further elucidate current study findings.

Results from Aim 3 similarly showed no differences in WMH volume between General Depression and Motivation/Withdrawal symptom profiles in individuals who endorsed at least one depressive symptom but did not meet clinical cutoffs. These results suggest that motivation and withdrawal symptoms may be linked to WMH even at subthreshold levels of depression. Findings are consistent with prior work demonstrating similar neuroanatomical correlates in clinical and subthreshold depression (Allan et al., 2016). Results from Aim 3 further suggests that findings from Aim 2 are not driven by clinical depression given the same pattern of results. However, it is important to keep in context when interpreting these results that the majority of participants fell below the clinical range on the GDS-15 (range 0-4); and thus, observed patterns in Aim 2 may not be reflective of clinical levels of depression at all. The lack of a sizeable number of participants with clinical depression precluded the separate

investigation of differences in WMH across identified symptom profile in a clinical sample.

4.3 Cortical Volume and Symptom Profiles of Late-Onset Depression

Across the full and subthreshold samples, exploratory analyses did not show significant differences in frontal and temporal brain volume across symptom profiles. While there have been some negative studies, neuroimaging studies in late-life depression have generally reported volumetric changes in frontal and temporal brain regions, most consistently in specific subregions rather than total frontal and temporal lobe volume (Naismith, Norrie, Mowszowski, & Hickie, 2012). Reductions in the orbitofrontal cortex, anterior cingulate cortex, and hippocampus have been shown in older adults with depression relative to non-depressed older adults (Dotson et al., 2009; Kumar, Bilker, Jin, & Udupa, 2000; Lavretsky, Roybal, Ballmaier, Toga, & Kumar, 2005; Taki et al., 2005; Taylor et al., 2020), with similar volumetric reductions in late-onset depression (Andreescu et al., 2008), although hippocampal dysfunction may be specifically associated with recurrent and early-onset depression (Bell-McGinty et al., 2002; MacQueen et al., 2003).

Our findings of white matter correlates without gray matter changes are somewhat unexpected, as several studies have shown a relationship between WMH burden and atrophy in the temporal and frontal lobes (Fiford et al., 2017; Raji et al., 2012; Tuladhar et al., 2015; Wen, Sachdev, Chen, & Anstey, 2006). Our current findings are consistent with previous literature that failed to find gray matter changes in relation to symptom dimensions of depression, despite significant WMH associations observed within the same study (Allan et al., 2016; Sexton et al., 2012); however, these studies

also examined total regional gray matter volumes akin to the current study. Prior work has suggested that WMH-related cortical atrophy may be tied to specific brain regions including orbitofrontal, anterior, medial and inferior temporal regions (Habes et al., 2016). As described above, the focus in the current study on total lobular volume rather than volume of subregions may explain current study findings.

4.4 Symptom Dimensions of Late-Onset Depression

Our results confirm an association between WMH and symptom dimensions of depression in older adults. Depressed mood and motivation/withdrawal depressive symptoms were significant predictors of WMH volume, which is consistent with prior research showing a relationship between depressive symptom dimensions and white matter changes. Consistent with our findings, Kirton et al. (2014) found significant associations between white matter lesions and the depressed mood and somatic subscales of the CES-D, while lack of positive affect was not significantly associated. While the somatic subscale of the CES-D largely assessed somatic symptoms, three items (e.g., “I could not get going”, “everything I did was an effort”, “I talked less than usual”) were similar in kind to motivation/withdrawal subscale items on the GDS-15, suggesting that motivation and withdrawal symptoms may be associated with white matter lesions as well. Other studies have similarly reported relationships between WMH and depressed mood, somatic, motivation and withdrawal symptoms (Dotson et al., 2013; Lavretsky et al., 2008), however, a relationship between positive affect in depression and white matter changes have not been reported, or were not consistently assessed separate from a general affective symptom dimension (Pujol et al., 2000).

In contrast to WMH volume, depressed mood and motivation/withdrawal symptoms were not significant predictors of frontal and temporal brain volumes, while positive affect was a marginal predictor of temporal lobe volume, but not frontal lobe volume. McLaren and colleagues (2017) have previously reported associations between lack of positive affect subscale scores on the CES-D and brain volume in regions of the temporal lobe (i.e., left inferior temporal lobe, right paracentral and left superior temporal gyrus); however, associations were also found for depressed mood and somatic symptom subscale scores, inconsistent with current study findings. A number of studies have reported changes in gray matter volume in frontal and temporal subregions as a function of depressive symptom severity, even at subthreshold levels (Kumar et al., 1997; McLaren et al., 2017; Osler et al., 2018; Szymkowicz et al., 2016; Webb, Weber, Mundy, & Killgore, 2014). Current study findings may suggest that positive affect depressive symptoms may be related to volumetric changes rather than WMH changes; while depressed mood, motivation, withdrawal symptoms are associated with the reverse pattern – WMH but not gray matter volume changes.

4.5 Strengths and Limitations

The current study has several limitations that should be considered. First, this study used archival data from the NACC data repository which limited the extent of mood, medical and brain imaging data that was available and used in the current study. For example, somatic illness is associated with depressive symptoms in older adults (Hegeman et al., 2015) but the presence of somatic illness and physical changes were not systematically collected in the NACC database. This limited our ability to quantify and control for the potential influence of somatic problems on depressive symptoms in

this study. Anxiety, which is often comorbid with depression was not also consistently and adequately assessed in the NACC. The self-report questionnaire Neuropsychiatric Inventory Questionnaire (NPI-Q) was used to assess the presence of anxiety, and clinical diagnosis of anxiety was not implemented until Version 3 of the Uniform Data Set in 2005 (Besser et al., 2018).

In addition, only the overall WMH volume in the brain was calculated and provided in the NACC Imaging database. There is evidence that depression may differentially relate to WMH based on type (i.e., periventricular or deep WMH) and location (Tham, Woon, Sum, Lee, & Sim, 2011). Studies have found that deep WMH but not periventricular WMH were strongly associated with depressive symptoms (Krishnan et al., 2006; Sneed & Culang-Reinlieb, 2011). Furthermore, prior work has shown that greater deep WMH in frontal lobe distinguished individuals with late-life depression from non-depressed older adults (Firbank, Lloyd, Ferrier, & O'Brien, 2004; Thomas et al., 2002). Under ideal conditions, diagnoses of somatic illness as well as medication would be collected, a stand-alone measure of anxiety severity and clinical diagnosis would be obtained, and a more extensive delineation of WMH would be calculated.

Second, the study sample was predominantly White, well-educated, without clinical depression, and with relatively low WMH burden which may limit generalizability of findings to older adults with more severe levels of depression and diverse backgrounds. Given the restricted sample of individuals with clinical depression, it may be possible that identified symptom profiles are representative of subthreshold depressive symptoms. It could be the case that a symptom profile distinguished by depression severity is more characteristic of clinical depression consistent with Hybel et

al. (2011; 2009) studies, and the low severity of depressive symptoms in the current study limited more extensive findings. We did identify a symptom profile characterized by more severe and broad endorsement of all depressive symptoms, and all individuals with this profile fell within clinical range. Future studies should explore symptom profiles using latent class analysis in individuals with clinical depression.

Third, with regard to statistical methodology, latent class models are based on conditional probability and are therefore open to classification error. For example, if the probability of an individual's item endorsements is highly similar across latent classes, this increases the likelihood of misclassification. In this study, we chose to estimate an asymptomatic latent class given the very low ratings on the GDS-15. The estimation of the asymptomatic class altered the classification accuracy of the Motivation/Withdrawal latent class as individuals placed in this class also had a 29.5% chance of belonging to the asymptomatic class. This potential for misclassification did not fall within an unacceptable range for classification accuracy, as entropy values fell above acceptable cutoffs (entropy >.6), suggesting adequate group separation (Asparouhov & Muthén, 2014). Entropy values around .80 are generally preferred and considered to be indicative of excellent classification; however, our class solution was bolstered by findings of distinct structural brain differences between Asymptomatic and Motivation/Withdrawal latent classes. Findings need to be tested and replicated in a different sample to examine the stability and generalizability of the class solution identified in the current study.

Finally, another limitation is the potential for selection bias. It is possible that primarily healthy people enrolled in the current study, as greater levels of depression,

physical and functional limitations may prevent study participation. Furthermore, individuals included in the current study sample were restricted to those who completed both the NACC-UDS and MRI visits. Participants are selectively screened to undergo MRI with criteria including but not limited to the ability to stay in the scanner for long periods at a time, below specified weight restrictions, which may have introduced bias.

The substantial strengths of this study mitigate these limitations. The large sample allowed for the use of advance statistical modeling to examine symptom-level differences in older adults. Furthermore, the use of person-centered methods allowed for a different approach to understanding depression at the symptom level. We were able to show *between* individual differences in symptom patterns of depression that provide insight into the different depressive symptoms that are most prominent for different individuals. Results may inform the identification of depressive symptoms in older adults, and can lead to the development of appropriate recommendations and interventions.

The current study included a sample of participants without a self-reported history of depression in earlier life. This allowed for a more focused investigation of WMH and depression in the context of empirical evidence of differences in etiology and symptom patterns between individuals with early- and late-onset depression (Krishnan, 2002; Rapp et al., 2005). The current study was able to identify a symptom profile characterized by motivation/withdrawal symptoms described in the literature as characteristic of vascular depression and late-onset depression (Salo et al., 2019)

An additional strength of the current study was the use of quantified WMH instead of visual ratings of WMH severity. Visual ratings of WMH depend on clinical

judgement by research staff or neuroradiologist and does not yield a true quantitative measure of WMH (Brickman et al., 2011). The use of quantified WMH allows for more accurate and reliable estimation of white matter lesion measurement.

5 CONCLUSIONS

The results from the current study demonstrate qualitatively distinct symptom profiles of depression in older adults, with the motivation and withdrawal symptom profile related to WMH volume, a marker of vascular abnormalities in the brain. In addition, the current study suggests that motivation and withdrawal symptoms are associated with WMH even at subthreshold levels of depressive symptoms. Findings from the current study underscore the importance of assessing depression at the symptom level and extend the literature by showing symptom patterns across individuals with meaningful correlates. These results highlight the clinical relevance of assessing symptom patterns in order to improve our identification of depressive symptoms in older adults, and better understand the nature of an individual's depression experience. This clinical approach differs from traditional over-reliance on diagnostic criteria that may not fully capture the depression presentation in older adults, and the sole use of cut scores on depression inventories during clinic visits. Future research studies should explore these symptom profiles in individuals with clinical depression and/or a wider range of depressive symptom severity, across diverse backgrounds, and examine WMH by type and location. Further work is also needed to identify appropriate recommendations and interventions for individuals with different symptom profiles with and without clinical depression.

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