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Neural Precursors of Apathy and Depressive Symptoms in Amnestic Mild Cognitive Impairment

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NEURAL PRECURSORS OF APATHY AND DEPRESSIVE SYMPTOMS IN AMNESTIC MILD COGNITIVE IMPAIRMENT

A Dissertation Presented

by

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ABSTRACT

NEURAL PRECURSORS OF APATHY AND DEPRESSIVE SYMPTOMS IN AMNESTIC MILD COGNITIVE IMPAIRMENT

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Depressive symptoms and apathy are common in amnestic mild cognitive impairment (aMCI) and are associated with increased risk of conversion to Alzheimer's disease (AD). The shared neuropathological model of neuropsychiatric symptoms (NPS) in AD suggests that symptoms of depression and anxiety represent noncognitive manifestations of neuropathological changes. Neurodegeneration in aMCI occurs in areas of the brain that support emotion regulation, including the limbic system and prefrontal control regions. Depression and apathy in aMCI have been linked to atrophy in the limbic system and prefrontal cortex and reduced connectivity in resting-state networks. However, it is not yet established whether neural changes in emotion centers in the brain predict symptoms of depression and apathy in persons with aMCI, or whether neural precursors in the limbic system and prefrontal cortex are associated with higher risk of conversion from aMCI to AD. The current study utilized longitudinal clinical and neuroimaging data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to determine whether change in neural structure and function in emotion centers predicted symptoms of depression and apathy in aMCI and conversion to AD. Depressive

symptoms and apathy increased over time, and cortical volume in emotion centers in the brain decreased over time, especially in the MCI group. The slope of change in neural markers was not correlated with the slope of change in depressive symptoms or with the presence versus absence of apathy. Presence of apathy, slope of change in depressive symptoms, and speed of atrophy in the amygdala and cingulate cortex predicted progression of disease. Overall, results provided limited support for the shared neuropathological model of NPS in aMCI, primarily related to amygdala atrophy. Future research is needed to further define the role of neurodegeneration in emotion centers in the brain in the development and/or worsening of NPS in aMCI.

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CHAPTER 1

INTRODUCTION

Amnestic mild cognitive impairment (aMCI) is a condition that often precedes Alzheimer's disease (AD; Xie et al., 2017; Ye et al., 2012). Estimates for the prevalence of aMCI in the older adult population range from 4 to 12% (Ganguli et al., 2004; Katz et al., 2012; Lopez et al., 2003; Peterson et al., 2010; Plassman et al., 2008) and between 11 and 17% of persons with aMCI convert to AD annually (Ganguli et al., 2004; Plassman et al., 2008). aMCI is associated with increased healthcare expenditures (Albert et al., 2002) and higher utilization of informal caregiving compared to cognitively healthy older adults (Zhu et al., 2013).

aMCI is characterized by memory impairment in the absence of significant functional impairment in activities of daily living (Peterson et al., 2009). Several markers for conversion from aMCI to AD are well established, including deficits in episodic memory (e.g., Ye et al., 2012), neuropathology of the medial temporal lobe (e.g., Dubois et al., 2016), and genetic factors (Jack et al., 2018). Emotion dysregulation—often indicated by depressive symptoms and apathy—is a less well understood marker for conversion from aMCI to AD. Knowledge about the neural precursors of depressive symptoms and apathy in persons with aMCI may augment our ability to predict who is at highest risk for progression to AD.

Emotion dysregulation is indicated by difficulty modulating the experience and expression of emotion (e.g., Gross, 2002). Emotion dysregulation manifests in depressive symptoms and apathy in the form of reduced ability to mount emotional responses and difficulty modulating negative affective states. Depressive symptoms and apathy in

persons with aMCI may result from neuropathological changes in regions of the brain that support emotion responding and regulation. Indeed, neurodegeneration in aMCI and AD occurs in regions of the brain that are known to support emotion regulation, including the amygdala, insula, anterior cingulate cortex (ACC), and prefrontal cortex (PFC; Karas et al., 2004; Killiany et al., 2000; Prieto del Val et al., 2016). Neural changes in aMCI involve both structural decline (e.g., grey matter atrophy) and functional disruptions (e.g., decreased or increased activity within and between networks).

It is well-established that the neuropathology of AD (e.g., atrophy in the medial temporal lobes, especially the hippocampus) precedes clinically-apparent memory decline. It is not yet clear if neural changes predict clinically-apparent symptoms of apathy and depression in aMCI. Additionally, it is not clear whether change in such neural markers is associated with progression from aMCI to AD. The present study addresses these gaps in the literature by investigating the longitudinal associations between neural changes in emotion centers of the brain and change in symptoms of depression and apathy. If we are able to identify early neural markers of increase in symptoms of depression and apathy in aMCI, this may improve our ability to predict who is at risk for clinically-apparent symptoms of depression and apathy. The present study will also address whether early neural markers of depression and apathy are predictive of conversion from aMCI to AD. Findings may identify subgroups of persons with aMCI that would benefit most from preventative interventions for neuropsychiatric symptoms (NPS) and cognitive decline.

1.1 Apathy and Depressive Symptoms in Persons with aMCI

Apathy is defined by a lack of motivation and/or interest in daily activities (Marin, 1990). Depressive symptoms include sadness, irritability, hopelessness, decreased positive affect, social withdrawal, and loss of energy (American Psychiatric Association, 2013). Apathy and depressive symptoms are common in neurological populations and are often co-morbid, but are conceptualized as distinct neuropsychological constructs (e.g., Levy et al., 1998). Surprisingly, though, there is substantial overlap in the neural correlates of depressive symptoms and apathy in older adult samples. Specifically, both depressive symptoms and apathy have been linked to reduced grey matter volume in the ACC (e.g., Bruen et al., 2008; Disabato & Sheline, 2012) and to reduced DMN connectivity (e.g., Joo et al., 2017; Wu et al., 2011). This overlap in the correlates of apathy and depression may be at least in part due to commonalities in the way the constructs are operationalized and measured (Mortby et al., 2012). Confounding of symptoms of apathy and depression in prior research has likely contributed to a lack of clarity with regard to distinct neural correlates. Depressive symptoms and apathy are conceptualized as transdiagnostic markers of emotion dysregulation in aMCI in the current study because the extant literature limits our ability to delineate the distinct neural correlates of these symptoms.

Apathy and depressive symptoms are the most commonly reported NPS in aMCI (e.g., Apostolova & Cummings, 2008). Approximately 26-50% of persons with aMCI exhibit depressive symptoms and 20-35% exhibit apathy (Di Iulio et al., 2010; Geda et al., 2008). Further, these symptoms are highly comorbid; between 37% and 58% of persons with MCI that report apathy also report depressive symptoms (Chilovi et al.,

2009; Zahodne & Tremont, 2013). Depressive symptoms and apathy are distressing for persons with aMCI and for their caregivers (Ryan et al., 2012; Teng et al., 2012) and are more predictive of quality of life than cognitive impairment (Ready et al., 2004; Teng et al., 2012). Further, NPS in AD are associated with higher informal care costs (Rattinger et al., 2019) and risk for institutionalization (Okura et al., 2012).

Apathy and depressive symptoms in aMCI are associated with a higher likelihood of conversion to AD (Lu et al., 2009; Mallo et al., 2020; Modrego & Ferrandez, 2004; Palmer et al., 2010; Richard et al., 2012; Ruthirakuhan et al., 2019; Van der Mussele et al., 2014). More generally, persons with aMCI that were classified as having affective symptoms were twice as likely as persons without affective symptoms to convert to AD (Forrester et al., 2016). Further, affective dysregulation added prognostic accuracy for development of MCI and AD above hippocampal atrophy (Gill et al., 2020).

1.2 Etiology of Neuropsychiatric Symptoms in aMCI and AD

There are several theories about the neurobiology of NPS in AD. The etiological model posits that NPS lead to the development of AD; the reactive model suggests that NPS develop as a psychological reaction to AD; the interactive model predicts that NPS and other risk factors interact to cause AD; and the shared neuropathology model hypothesizes that NPS reflect noncognitive manifestations of AD neuropathology (Geda et al., 2013; Porsteinsson & Antonsdottir, 2015). The shared neuropathology model provides a useful framework for investigating the etiology of NPS in aMCI, as it mirrors well-supported models of the neurobiology of cognitive decline in persons with aMCI and AD (e.g., Blasko et al., 2008; Ferreira et al., 2011; Li et al., 2016; Whitwell et al., 2008). That is, neuropathological changes in the medial temporal lobe lead to initial

decline in memory, followed by more general decline in cognitive and functional abilities as neurodegeneration progresses and affects additional structures and circuits. Based on the shared neuropathological model, neuropathological changes in structures and circuits of the brain that support emotional function (e.g., the limbic system and frontal lobes) occur in aMCI; NPS arise—at least partially—as a result of the same neuropathological changes that cause cognitive decline and functional impairment. According to this model, NPS in AD reflect non-cognitive manifestations of the underlying neuropathology of the disease. The shared neuropathology model offers the potential to develop an integrative theory of the neurobiology of diverse symptoms (e.g., cognitive decline, NPS) in aMCI.

Empirical evidence for the shared neuropathology model of NPS in AD remains limited (Van Dam et al., 2016). This model has only been applied in AD and has not been tested in persons with aMCI. AD neuropathology begins well before the onset of clinically-apparent symptoms, and neuropathological changes in emotion centers in the brain are apparent even in aMCI (e.g., Csukly et al., 2016; Killiany et al., 2000; Yi et al., 2016). The shared neuropathological model of NPS in AD implies that NPS are a consequence of neurodegeneration, which may help explain the association between NPS and risk for conversion to AD. That is, the presence of NPS may signal more advanced neuropathology, or neuropathology in key regions, in aMCI.

1.3 Neurobiology of Emotion Dysregulation in aMCI

During emotion regulation in healthy older adults, the amygdala and insula are activated in response to emotional stimuli, and emotional arousal is hypothesized to be modulated and down-regulated by cognitive control regions, such as the ventromedial prefrontal cortex (vmPFC), ventrolateral medial prefrontal cortex (vlPFC), and anterior

cingulate cortex (ACC; Dolcos et al., 2014; Mather, 2016; Winecoff et al., 2011). Effective emotion regulation thus involves the mounting of an emotional response by subcortical limbic structures and appropriate modulation of negative emotional states by cognitive control regions (e.g., Green & Mahli, 2006; Ochsner et al., 2012). Emotion regulation is also supported by the default mode network (DMN), which encompasses the posterior cingulate cortex (PCC), medial PFC, and medial temporal lobes (e.g., Gusnard & Raichle, 2001; Raichle et al., 2001). The DMN is implicated in self-reflective processing and emotion awareness (e.g., Martins & Mather, 2016; Prakash et al., 2013) and supports aspects of emotion regulation that involve assigning personal meaning to stimuli and situations. Inversely, emotion dysregulation occurs as the result of disturbance in one or more of the component parts of the emotion regulation system. Difficulties with emotion dysregulation may occur as the result of damage to the hardware (e.g., structural atrophy) or software (e.g., reduced functional connectivity) of the emotion regulation system.

Neurodegeneration in aMCI occurs in a number of areas of the brain implicated in emotion dysregulation. Significant gray matter atrophy is found in the amygdala (Csukly et al., 2016; Poulin et al., 2011; Yi et al., 2016), insula (Karas et al., 2004), ACC (Killiany et al., 2000), and PCC (Bailly et al., 2015; Trivedi et al., 2006) in persons with aMCI. Atrophy in these areas of the brain likely undermines the ability to effectively regulate emotions.

In addition to structural changes, persons with aMCI demonstrate functional changes in neural regions associated with emotion dysregulation. Persons with aMCI exhibit lesser spontaneous activity in the medial PFC compared to healthy controls (Cai

et al., 2017; Ren et al., 2017). In persons with aMCI relative to controls, increases and decreases in spontaneous activity in the amygdala (Cai et al., 2017; Han et al., 2012) and ACC are observed (Gold et al., 2010; Ren et al., 2017), which may indicate less stability in emotion function in persons with aMCI. Compared to healthy older adults, persons with aMCI demonstrate decreased functional connectivity within the DMN (Cai et al., 2017; Joo et al., 2017; Palmqvist et al., 2017; Wang et al., 2012; Yi et al., 2015). Persons with aMCI also exhibit reduced functional connectivity between the amygdala and prefrontal/fronto-parietal areas (Ortner et al., 2016).

1.4 Neurobiology of Depressive Symptoms and Apathy in aMCI

Emotion dysregulation is a multifaceted construct that encompasses difficulties with the generation, expression, and modulation of emotion (e.g., Mennin et al., 2007). Emotion dysregulation, in its many forms, makes up a core component of many psychiatric disorders (e.g., Bradley et al., 2011). When examined from a lifespan developmental perspective, emotion dysregulation appears to serve as a mechanism for the development of psychopathology (Cole et al., 2008). Observed NPS (e.g., apathy, depressive symptoms) are thus—at least in part—a reflection of dysregulated affective processes. In order to definitively determine the neural mechanisms of NPS in aMCI and AD, it will be necessary to study the direct links between specific neural structures and circuits, aspects of emotion dysregulation, and the symptoms that arise as a result of these pathways. The extant knowledge base is far from this eventual goal. However, NPS have proven to be useful proxy variables to begin to delineate links between neural changes in aMCI and development of NPS.

Apathy and depressive symptoms both reflect aspects of emotion dysregulation. Both conditions reflect emotion dysregulation via blunting of affective responses and reduced goal-directed behaviors, and depressive symptoms additionally involve difficulty modulating negative affect states. Both apathy and depressive symptoms can be conceptualized to reflect "negative" symptoms in that they typically involve the absence of wanted behaviors, resulting in negative outcomes (e.g., flat affect, withdrawal, isolation).

The neural structures and circuits that are implicated in the development of symptoms of depression mimic those that are involved in emotion dysregulation more generally. The cognitive-biological model of depression posits that depressive symptoms involve decreased mounting of emotional responses (e.g., hypoactivity in the amygdala) and lesser down-regulation of negative emotions (e.g., atrophy or hypoactivity in the PFC; Disner et al., 2011). Persons with aMCI and depressive symptoms demonstrate greater atrophy in frontal white matter volume relative to persons with aMCI without depressive symptoms (Lee et al., 2012). Depressive symptoms are associated with frontal lobe dysfunction (i.e., lower glucose metabolism in the frontal superior gyrus) in persons with AD (Lee et al., 2006).

Late-life depression is associated with atrophy in the amygdala and ACC (Disabato & Sheline, 2012) and in the PCC (Ries et al., 2009). Additionally, depressive symptoms in older adults are associated with reduced activity in the frontal lobes (Viitanen et al. , 2007) and reduced activity in the vmPFC during emotional tasks (Brassen et al., 2008). Late-life depression is also associated with reduced DMN connectivity (Wu et al., 2011).

The neural structures and circuits implicated in symptoms of apathy also demonstrate overlap with regions involved in emotion dysregulation more generally. Apathy is linked to atrophy in the bilateral ACC in persons with aMCI and AD (Apostolova et al., 2007; Bruen et al., 2008; Stanton et al., 2013), and to atrophy in frontal-subcortical circuits in MCI (Johansson et al., 2020) and AD (Starkstein et al., 2014). Apathy is associated with lower functional connectivity in the DMN (Joo et al., 2017), reduced blood flow in the frontal lobes as measured by PET imaging (Kazui et al., 2017), and hypometabolism in the PCC (Ng et al., 2019) in persons with aMCI. Affective dysfunction, particularly apathy, is associated with decreased functional connectivity in the frontal-parietal control network in persons with aMCI (Munro et al., 2015).

Studies of the neural correlates of apathy in older adult and late-life depression samples provide additional evidence for the role of the ACC and PCC in apathy. In older adults without cognitive impairment, symptoms of apathy are associated with reduced grey matter volume in the ACC (Lavretsky et al., 2007). Associations between apathy and gray matter atrophy in the ACC and dorsolateral PFC are found in a variety of neurological and psychiatric populations, including AD (Kos et al., 2016). Among persons with late-life depression, those with symptoms of apathy evidence greater tau and amyloid burden in the ACC, indicating higher risk for development of AD (Eyre et al., 2017). Improvements in apathy in geriatric depression are associated with greater volume in the PCC (Yuen et al., 2014).

To date, most studies that have examined neural correlates of apathy and depressive symptoms in aMCI have focused on cross-sectional comparisons between healthy controls and persons with aMCI. One longitudinal study examined the link

between neural changes and depressive symptoms in persons with aMCI. Gonzales et al. (2017) found that persons with stable subsyndromal depression in aMCI displayed more accelerated cognitive decline than those without depressive symptoms, which was accounted for by gray matter atrophy in the ACC and frontal lobes. Thus, there is preliminary support for the utility of examining change in neural structures in relation to depressive symptoms and progression of disease in aMCI. Whereas Gonzales et al. (2017) focused on depressive symptoms as a risk factor for disease progression, they did not address the timing of change in neural structures versus change in symptoms of depression. The current study will build on the findings of Gonzales et al. (2017) by focusing on the temporal associations between change in neural markers and change in symptoms of both apathy and depression.

1.5 The Present Study

Despite the prevalence and adverse consequences of depressive symptoms and apathy in persons with aMCI, the neurobiology of these symptoms is not yet established. The shared neuropathological pathway model suggests that depressive symptoms and apathy may arise as a result of early neuropathological changes. However, it is not yet clear whether neural changes precede symptoms of depression and apathy in aMCI, or whether identification of neural changes may increase our ability to predict development of affective symptoms and conversion from aMCI to AD. Using longitudinal behavioral and neuroimaging data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), the first aim of this study was to determine longitudinal associations between changes in neural structure and function of key emotion regions and circuits, and depressive symptoms and apathy in persons with aMCI and AD. Depressive symptoms and apathy in

persons with aMCI and AD are hypothesized to be associated with atrophy and reduced resting-state connectivity in core emotion centers in the brain (i.e., amygdala, ACC, and PCC, and reduced resting-state connectivity within the DMN), and it is expected that these changes will be associated with worsening of depressive symptoms and apathy. The neural regions and circuits of interest are derived from well-established neural correlates of affective dysregulation in old age (e.g., Dolcos et al., 2014; Mather, 2016; Winecoff et al., 2011) and from structural and functional changes associated with depression and apathy in aMCI and AD (e.g., Bruen et al., 2008; Joo et al., 2017; Lee et al., 2012; Starkstein et al., 2014). The second aim of the current study was to determine whether change in neural structures and circuits of interest (i.e., amygdala, ACC, PCC, and DMN) predicts higher likelihood of progression of disease (i.e., CN to MCI or MCI to AD). Results from the current study will help delineate the temporal association between neural changes and symptoms of apathy and depression. If hypotheses are supported, results may be consistent with the shared neuropathology model of NPS in aMCI.

CHAPTER 2

METHOD

2.1 Data Source

Data for the current study were obtained from the ADNI database (adni.loni.usc.edu). ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI is to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of aMCI and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

2.2 Participants

All ADNI participants are between the ages of 55 and 90 at enrollment. Participants are assigned to study groups based on performance on the Mini-Mental Status Exam (MMSE), Wechsler Memory Scale Logical Memory II (WMS LMII), and Clinical Dementia Rating (CDR). Cognitively normal (CN) participants score in the normal range on the MMSE, WMS LMII, and CDR and report no memory complaints or functional deficits. aMCI participants score in the normal range for the MMSE, score 0.5 on the CDR, demonstrate abnormal performance on WMS LMII, and report a memory complaint. At each study visit, diagnosis is coded categorically (i.e., CN vs. MCI vs. AD), and any diagnostic change is noted. Inclusion criteria for all participants are fluency in English or Spanish, at least a 6^{th} grade education, and a score less than 6 on the GDS at entry into the study. Exclusion criteria for all participants include diagnosis of any

neurologic disease (other than suspected AD for the MCI group); evidence of infection, infarction, or focal lesions on the screening MRI; diagnosis of Major Depressive Disorder within the prior two years; history of schizophrenia; and diagnosis of substance or alcohol abuse within the prior two years. Additional inclusion criteria for the current study are data were at least two 3T MRI scans that passed quality control evaluation and at least two timepoints with NPS ratings to allow for longitudinal analyses, resulting in 563 eligible subjects (n = 224 CN; n = 339 MCI; Figure 1). CN and MCI subjects did not differ in age at baseline and had similar education attainment. Compared to the CN sample, MCI subjects were more likely to identify as male, White, and Non-Hispanic/Latino (see Table 1). The majority of subjects (66%) had at least two years of follow-up (range: 0.5-8 years); mean years of follow-up was significantly longer in the CN than the MCI group (Table 1).

2.3 Measures

2.3.1 Cognitive Screening

The MMSE is a brief measure of global cognitive function (Folstein et al., 1975). The MMSE assesses orientation, attention, recall, language, and the ability to follow simple verbal commands. The MMSE demonstrates excellent test-retest reliability when administered from 24 hours to 28 days apart (rs = .83 to .98; Folstein et al., 1975). Concurrent validity of the MMSE is demonstrated via large correlations with verbal and performance IQ scores on the WAIS (rs = .66 to .78). The MMSE effectively identifies persons with cognitive impairment with high sensitivity (80%) and specificity (100%; Schramm et al., 2002). All CN and MCI participants scored in the normal range on the

MMSE at enrollment (i.e., 24-30). In the current sample, the CN group scored significantly higher on the MMSE than the MCI group at baseline (Table 1).

2.3.2. Dementia Rating

The Clinical Dementia Rating (CDR) scale (Morris, 1997) was developed to evaluate the severity of dementia. The CDR assesses the extent of deficits in memory, orientation, judgment, problem-solving, community and domestic activities, and personal care. The CDR demonstrates good interrater reliability (ICC > 80%), concurrent validity (*r*s range from .30-.70 across studies), and strong diagnostic validity (Olde Rikkert et al., 2011). In the current sample, the CN group scored significantly lower on the CDR at baseline than the MCI group (Table 1).

2.3.3 Apathy

Apathy was assessed at baseline and each mid-year study visit with the apathy/indifference item on the Neuropsychiatric Inventory Questionnaire (NPI-Q; i.e., "Does the patient seem less interested in his/her usual activities or in the activities and plans of others?"; Kaufer et al., 2000). The NPI-Q is a brief self-administered questionnaire. Informants indicate the presence versus absence of 12 neuropsychiatric symptoms in the prior 4 weeks; for endorsed items, informants subsequently rate the severity of the symptom on a three-point scale (i.e., 1 = mild, 2 = moderate, 2 = severe). The NPI-Q demonstrates excellent test-retest reliability (r = .80 for total symptom count; r = .94 for symptom severity score) and convergent validity via strong correlations with the original interview form of the NPI (*r*s = .71-93 for individual symptoms; Kaufer et al., 2000).

2.3.4 Depressive Symptoms

Depressive symptoms were assessed at baseline and at each yearly study visit using the Geriatric Depression Scale Short Form (GDS-SF; Sheikh & Yesavage, 1986). The GDS-SF is a 15-item self-report measure specifically developed to measure depression in older adults; items are rated on a "yes/no" basis. The GDS-SF was adapted from the original 30-item GDS (Brink et al., 1982), which exhibits excellent internal consistency (alpha = .94), split-half reliability (r = .94), and test-retest reliability (r = .85; Yesavage et al., 1983). The GDS-SF is highly correlated with the original GDS (I = .84, I < .001) and is able to differentiate depressed from non-depressed older adults, including those with mild to moderate dementia (Sheikh & Yesavage, 1986). The GDS-SF demonstrates good concurrent validity via strong correlations with other measures of depression (Herrmann et al., 1996). In the current sample, baseline GDS-SF scores were higher in the MCI group than the CN group, although both groups were well below the clinical cutoff for depression (Table 1).

2.4 Procedures

Participants enrolled in ADNI undergo an initial screening assessment, during which demographic, clinical, medical, and neuropsychological information is collected. Participants also undergo a baseline 3T fMRI within two weeks of the initial screening visit. Subsequent study visits are conducted at every six months from baseline. The MMSE, CDR, and GDS were administered at the annual visits, along with structural and functional MRI scans. The NPI-Q was administered at mid-year visits.

2.5 Imaging Procedures

All scans were conducted on a 3T scanner. Participants were screened for standard MRI precautions. The scan procedures consisted of the following sequence: localizer, sagittal MP-RAGE, accelerated MP-RAGE, resting state fMRI (with eyes open), axial T2-FLAIR, axial T2-Star, axial ASL perfusion, axial DTI scan. All scans were reviewed for quality control at Mayo Clinic.

2.5.1 Imaging Pre-processing

Standardized imaging datasets were used for structural and functional imaging analyses. Within these standardized datasets, all MPRAGE images were pre-processed using gradient warping, scaling, B1 correction, and N3 inhomogeneity correction by Mayo Clinic. Pre-processed structural images were then run through FreeSurfer version 5.1 using longitudinal processing. This approach allows for registration of images to a within-subject template space. Longitudinal processing steps included motion correction and registration, non-uniform intensity normalization, Talairach transform computation, intensity normalization, and segmentation. For the current study, cortical volume measures for the amygdala, caudal ACC (cACC), rostral ACC (rACC), and PCC were derived from standardized structural MRI datasets.

Additional preprocessing of functional MRI data included the following steps: discarding the first 3 volumes, slice time correction, realignment, normalization to SPM5 EPI template, smoothing with 4 mm full-width half maximum Gaussian kernel, linear detrending to correct for signal drift, and 0.01-0.08 Hz bandpass filtering. Linear regression correction included rigid body transformation motion effects. DMN connectivity was derived by extracting the average time course for each ROI (i.e.,

anterior DMN [aDMN] and posterior DMN [pDMN]) and comparing to the time course of each voxel within the respective ROI using Pearson's product-moment correlation coefficient. The median ROI-to-voxel (RV) correlation within each ROI was extracted; the aDMN parameter was divided by the pDMN correlation, creating the DMN RV-ratio.

CHAPTER 3

DATA ANALYTIC PLAN

Due to the nested structure of the data (i.e., repeated measures at Level 1 nested within individuals at Level 2), I utilized multilevel longitudinal structural equation models to address study aims. Typical GLM-based analyses used for imaging studies cannot account for the repeated measures of longitudinal data, so Level 1 parameter estimates for imaging variables were obtained from standardized ADNI imaging datasets and used in parallel process latent growth models and lagged analyses in Mplus version 8 (Muthen & Muthen, 1998-2012). Parallel process latent growth models and lagged analyses address the study aims from two vantage points. Parallel process models establish whether change in neural markers is associated with change in symptoms of depression or apathy, whereas lagged analyses allow for determination of temporal precedence of neural markers vs. behavioral symptoms. Results from these analyses provide complimentary data about the nature and timing of associations between neural precursors and symptoms of depression and apathy in aMCI.

To investigate Aim 1 (i.e., whether longitudinal change in neural markers is associated with longitudinal change in depressive symptoms and apathy), I first conducted parallel process latent growth models, in which latent growth factors are estimated for the predictor (e.g., grey matter volume in the amygdala) and outcome (e.g, depressive symptoms). For the current study, parallel process models are useful because they estimate associations between change in variables over time (Madhyastha et al., 2018; Telzer et al., 2018); these models addressed whether neural changes over the course of the study are associated with change in symptoms of depression and/or apathy.

In parallel process models, the primary outcome of interest was the association between latent growth factors for the predictor and outcome. That is, models determined whether there were associations between change in neural structure/function and change in symptoms of depression or apathy.

In order to determine whether change in neural variables and symptoms of depression/apathy are specific to neuropathological changes in aMCI/AD, I included group as a between-group covariate in parallel process models. Participants were divided into (1) those that entered the study as CN and remained CN for all study visits, and (2) those that started as MCI or progressed from CN to MCI or AD during the study (i.e. cognitively impaired [CI] group). If slopes of change in neural markers and NPS are steeper in the CI group than in the CN group, this would provide conceptual support for a specific role for disease-related neurodegeneration in the disruption of emotion circuits and development of NPS in aMCI and AD, versus typical brain and behavior changes over time in older adults.

Parallel process models are not able to directly address the temporal course of change in neural structures/function and change in symptoms of depression or apathy; I thus conducted lagged analyses to determine the specific temporal course of the association between neural changes and change in symptoms of depression and/or apathy. Lagged models determine whether variables predict themselves at later timepoints, and/or whether they predict other study variables at later timepoints. Though these models cannot determine causality, they can provide conceptual support for temporal precedence between variables. If hypotheses are supported for lagged analyses, these models will suggest that earlier neural volume and connectivity predict later symptoms of apathy and

depression. This result would be consistent with models of the neurobiology of NPS in aMCI and AD that posit that NPS may arise as a result of neural changes in emotion centers in the brain. I also concurrently tested alternate theories of the etiology of NPS in aMCI and AD in addition to the shared neuropathology model. I included predictive pathways from behavioral variables to neural variables; significant pathways in these models would provide evidence consistent with the etiological model of NPS (i.e., that NPS contribute to the development of aMCI/AD neuropathology). If both neural and behavioral variables predict each other at later time point, this would suggest a more complex picture of the neurobiology of apathy and depressive symptoms in aMCI in which neural changes and NPS form a feedback loop that compounds risk for worsening symptoms and progression of disease.

I addressed Aim 2 (i.e., whether neural precursors are associated with disease progression) using parallel process models. I added an additional binary outcome variable (i.e., conversion to MCI or AD) to parallel process models to determine if growth in depressive symptoms and/or neural variables was associated with higher likelihood of conversion to MCI or AD.

CHAPTER 4

RESULTS

4.1 Preliminary Analyses

Descriptive statistics were examined to evaluate the data for normality and outliers. There was a significant, but small, positive correlation between depressive symptoms and apathy at baseline ($\rho = .26$ $p < .001$), supporting the inclusion of depressive symptoms and apathy as distinct outcomes in analyses. Age was included as a covariate due to significant correlations with the outcome variables, which included depressive symptoms, apathy, and conversion of disease ($p < .05$; Table 2). Patient education was included as an additional covariate due to a significant group difference in education attainment between baseline CN and baseline MCI groups (Table 1).

Data were transformed where appropriate to approach normality. Scores on the GDS were log-transformed due to significant positive skew. Endorsement of apathy was rare, with limited variability in severity ratings, creating a significantly positively-skewed distribution; apathy scores were dichotomized to reflect the presence versus absence of apathy at each timepoint. Bilateral cortical volume measurements were averaged to create a single measure of cortical volume for each neural structure of interest. Variables were scaled when appropriate to enable Mplus analyses.

4.2 Longitudinal Associations Between and Neural Markers and NPS

To address Aim 1—whether change in neural markers is associated with change in depressive symptoms and/or apathy—parallel process models were conducted that estimated concurrent growth curves for depressive symptoms and each neural marker

(Table 3; Figure 2). Ten separate models were planned for each combination of predictor (i.e., amygdala, cACC, rACC, and PCC volume; DMN connectivity) and outcome variable (i.e., depressive symptoms, apathy). However, the majority of subjects (84.9%) did not display variance in apathy scores over time, resulting in inadequate variance to warrant estimation of a growth curve process for apathy scores. Thus, parallel process models were not conducted with apathy; instead, apathy was entered as a dichotomous variable at Level 2 (i.e., whether a person ever displayed apathy vs. not) in latent growth models to assess for differences in mean slope of change in neural markers based on the presence of apathy.

4.2.1 Baseline Group Differences

At baseline, the CI group (i.e., subjects who entered the study as MCI or who started as CN but progressed to MCI or AD) had a higher level of depressive symptoms than the CN group. Amygdala volume was significantly smaller in the CI than the CN group. There were no significant group differences in cACC, rACC, or PCC volume or DMN connectivity at baseline.

4.2.2 Growth in Variables Over Time

Symptoms of depression increased over time for the entire sample; the slope of change in depressive symptoms was not significantly different between CN and CI groups. There was a significant negative slope for amygdala, cACC, rACC, and PCC volume in the overall sample, and each of these associations were moderated by group such that the CI group demonstrated a significantly more negative slope than the CN group. That is, there was faster atrophy in neural structures involved in emotion

regulation in CI subjects compared to CN subjects. There was not a significant slope of change for DMN connectivity in the overall sample, nor significant change for either group.

4.2.3 Associations Between Growth Curves

Contrary to predictions, the slope of change in depressive symptoms was not significantly correlated with the slope of change in the amygdala, cACC, rACC, and PCC volumes or in DMN connectivity.

4.2.4 Moderation of Neural Slopes by Apathy

Due to a small number of subjects with apathy – and thus low variability of apathy both within and between subjects – parallel process models were not conducted with apathy. Instead, apathy was entered as a between-subject dichotomous variable (i.e. persons with apathy endorsed at one or more timepoints versus those without apathy at any timepoint) in latent growth models to assess for moderation of slope in neural markers. There was not a significant difference in slope for subjects with and without apathy for any of the neural targets (Table 4). That is, persons with apathy did not exhibit significantly greater change in neural structure or circuits over time than participants without apathy. Persons with apathy had smaller rACC volumes at baseline than persons without apathy.

4.2.5 Summary

Surprisingly, depressive symptoms increased over time for the whole sample, including cognitively normal subjects. As expected, atrophy in key regions (i.e.,

amygdala, cACC, rACC, PCC) was moderated by group such that persons with cognitive impairment demonstrated faster decline than persons with normal cognition. Contrary to predictions, there were no significant associations between the rate of atrophy in neural regions and the rate of increase in depressive symptoms. Similarly, apathy did not moderate the rate of atrophy in any of the neural regions.

4.3 Temporal Associations Between Neural Markers and NPS

Temporal precedence of neural markers and depressive symptoms and apathy was assessed with lagged predictor and outcome models. Separate models were planned for each combination of predictor and outcome variables, resulting in 10 models. However, lagged predictor and outcomes models as outlined above were not able to converge in models including apathy, so traditional cross-lagged models were used to assess for temporal precedence of neural precursors and apathy. Such models defined specific predictive pathways (e.g., whether amygdala volume at baseline predicted apathy scores at the next timepoint), rather than estimating an overall mean association between neural volume at the previous timepoint and current apathy scores.

4.3.1 Depressive Symptoms

As outlined above, temporal precedence of neural markers and depressive symptoms was assessed with lagged predictor and outcome models. These models allow for determination of whether there is an association between current depressive symptoms and prior neural volume, and vice versa. Amygdala volume and DMN connectivity predicted depressive symptoms at the subsequent timepoint (Table 5). No other neural markers predicted later depressive symptoms. Depressive symptoms also

predicted amygdala volume at the subsequent timepoint, indicating a bidirectional relationship.

4.3.2 Apathy

Cross-lagged panel models were conducted with apathy and neural markers due to failure of lagged predictor models to converge. In these models, both autoregressive and predictive pathways were estimated to determine the association between neural volume and apathy at the next timepoint, controlling for the influence of prior apathy. The data did not support inclusion of a group variable in these analyses, so models were run only in the CI group (i.e. persons that start the study as MCI or progress from CN to MCI during the study). A model including apathy and DMN connectivity did not converge due to insufficient observations, and was thus excluded from the planned analyses.

Stability paths for both apathy and neural markers were significant or trending for all models (Table 6). That is, earlier apathy scores predicted later apathy scores and earlier neural volumes predicted later neural volumes. Amygdala volume and PCC volume at six months predicted subsequent apathy scores. However, contrary to expectations, there was not a consistent pattern of earlier neural volume predicting later apathy scores.

4.3.3 Summary

There was partial support for the hypothesis that decline in key neural markers would predict subsequent increase in depressive symptoms and apathy. Specifically, lesser amygdala volume predicted greater depressive symptoms at the subsequent timepoint. However, the inverse was also true; greater depressive symptoms predicted

lesser amygdala volume at the subsequent timepoint. Greater DMN connectivity predicted greater depressive symptoms at the subsequent timepoint, contrary to predictions. Lesser amygdala and PCC volume at the six month visit predicted greater likelihood of apathy at the subsequent timepoint; however, this pattern was not replicated across any other timepoints.

4.4 Associations Between Growth in NPS and Neural Markers and Conversion

To assess Aim 2—whether change in depression, apathy, and neural markers is associated with greater likelihood of progression of disease—a between-subjects variable was added to parallel process models that separated subjects into those whose diagnosis stayed stable throughout the study and those who converted (i.e., CN to MCI or AD; MCI to AD). When entered into the model alone, the slope of change in depressive symptoms was significantly associated with greater likelihood of conversion (OR = 6.60, 95%CI: 1.15-37.71). That is, a more positive slope of change in depression over time was associated with a greater likelihood of progression of disease. Additionally, a higher likelihood of conversion was associated with greater atrophy over time in the amygdala (OR = 0.32, 95%CI: 0.21-0.49), cACC (OR = 0.55, 95%CI: 0.40-0.76), rACC (OR = 0.77, 95%CI: 0.60-0.98), and PCC (OR = 0.66, 95%CI: 0.56-0.79), but not DMN connectivity (OR = 9.96, 95%CI: 0.012-8046.56).

Growth curves could not be reliably estimated for apathy due to limited within-person variability. Thus, the direct association between change in apathy and conversion of disease was not assessed. However, persons with apathy at any point of the study (23.1% of sample) were more likely to progress than those without apathy, $\chi^2(1, N=563) = 43.38$, $p < .001$.

4.4.1 Summary

Consistent with predictions, the slope of increase in depressive symptoms and the rate of atrophy in key neural regions (i.e., amygdala, cACC, rACC, PCC) predicted likelihood of conversion (i.e., CN to MCI or MCI to AD). That is, greater rate of increase in depressive symptoms, and greater rate of atrophy in neural structures, predicted greater likelihood of disease progression. Additionally, as expected, the presence of apathy was associated with a greater likelihood of disease progression.

CHAPTER 5

DISCUSSION

The current study aimed to determine longitudinal associations between neuropathological changes in emotion centers in the brain and symptoms of depression and apathy in MCI. Consistent with expectations, there was some indication that decline in neural structures and circuits that support emotion function predicts increase in symptoms of depression and apathy. These results are intriguing because they provide preliminary support for the shared neuropathological model of NPS in MCI, which posits that symptoms of depression and apathy reflect noncognitive manifestations of underlying disease-specific neurodegeneration (Geda et al., 2013; Porsteinsson & Antonsdottir, 2015). Further, cortical volumes in emotion centers decreased more rapidly in persons who experienced cognitive impairment or cognitive decline than persons who remained cognitively stable. Faster atrophy in neural structures that support emotion function was associated with greater likelihood of progression of disease, both from normal cognition to MCI and from MCI to AD. Thus, early neuropathological changes in emotion circuitry may serve as prognostic markers for persons with aMCI.

5.1 Longitudinal Change in NPS and Neural Markers

Neurodegeneration may occur in emotion centers early in the AD disease process, even before onset of the cognitive symptoms that form the basis for diagnosis of aMCI (e.g., Peterson et al., 2009). As noted above, there was faster atrophy in the amygdala, ACC, and PCC in persons who progressed from cognitively normal to cognitively impaired than in persons who remained cognitive normal throughout the study.

In contrast, depressive symptoms were not a significant predictor of cognitive progression. Unexpectedly, depressive symptoms increased over time in persons who did and did not develop cognitive impairment. Increases in depressive symptoms over time were expected in persons with cognitive impairment because extant research supports increase in severity of depressive symptoms along the AD disease spectrum (e.g., Di Iulio et al., 2010). Increases in depressive symptoms were not expected in persons who remained cognitive stable. Indeed, there are well-established patterns of increased emotional well-being in healthy aging (e.g., Cacioppo et al. 2008; Carstensen et al., 2011; Mikels et al., 2014), although some studies report mixed findings, similar to the current data (e.g., Andreescu et al., 2008; Huang, et al., 2011). That both cognitively intact and cognitively impaired groups evidenced significant increase in symptoms of depression over time argues against a purely neuropathological etiology for depressive symptoms in MCI.

Delineating the etiology and impact of depressive symptoms on cognition in old adulthood has long proven challenging due to heterogeneity in the onset and nature of depressive symptoms (e.g., Fiske et al., 2009). It may be necessary to distinguish between new-onset depressive symptoms and exacerbation of long-standing depressive symptoms in late life in order to more accurately determine the prognostic value of depressive symptoms in early stages of AD. New-onset depressive symptoms are more likely to reflect incipient neurodegeneration than symptoms with onset earlier in life, which may be exacerbated by—but are less likely to be primarily caused by—neurodegeneration.

Consistent with prior findings (e.g., Guercio et al., 2015), symptoms of apathy were more prevalent among participants that entered the study with, or developed,

cognitive impairment than among participants that remained cognitively intact throughout. Apathy is common in many neurological disorders (e.g., Ishii et al., 2009), but is not common in otherwise healthy older adults. In contrast, depressive symptoms are less specific to neurological conditions and are more commonly found in otherwise healthy older adults without cognitive deficits. Group differences in apathy, but not depressive symptoms, may thus reflect the relative rarity of apathy in healthy older adults.

5.2 Associations Between Neural Markers and Neuropsychiatric Symptoms

Whereas there was evidence of atrophy in neural structures and increase in NPS over the course of the study, there was no evidence of concurrent associations between *change* in neural markers and *change* in symptoms of depression or apathy. Contrary to expectations, greater atrophy in neural markers was not associated with greater increase in depressive symptoms. Similarly, atrophy in neural markers was not different for persons with and without apathy.

In contrast, there was partial evidence for neural markers predicting later symptoms of depression and apathy. Specifically, lesser amygdala volume was associated with greater depressive symptoms a year later. Unexpectedly, the inverse of this relationship was also significant, such that greater depressive symptoms predicted lesser amygdala volume at the subsequent timepoint. Thus, associations between amygdala volume and depressive symptoms may be more accurately characterized as a feedback loop, rather than a linear relationship in which neural changes predict later symptoms of depression.

Another curious finding was that greater DMN connectivity predicted greater depressive symptoms at the subsequent timepoint, contrary to predictions. It is possible that greater DMN connectivity may reflect an increase in maladaptive self-reflective processes often seen in depression (e.g., rumination). However, prior findings about the association between DMN connectivity and depressive symptoms are mixed (Berman et al., 2014; Wang et al., 2012), and continued investigation is needed to determine whether the association between increased DMN connectivity and subsequent increase in depressive symptoms is replicated along the AD disease spectrum.

Whereas there was not a pattern of earlier neural markers predicting later symptoms of apathy, an isolated finding indicated that volume in certain neural structures (i.e., amygdala and PCC volume) at the six month visit significantly predicted presence of apathy at the one year timepoint. There is not a theoretical reason that these particular timepoints would reveal a significant relationship between atrophy and apathy, especially since participants entered into the study at different chronological times and with different levels of cognitive impairment. As will be discussed in more detail below, a sample with greater prevalence of apathy will be better suited to pursue this line of inquiry.

5.3 Association Between Depressive Symptoms, Apathy, and Progression of Disease

It is well-established that symptoms of depression in MCI are associated with risk for conversion to AD (e.g., Lu et al., 2009; Van der Mussele et al., 2014). The current study similarly found an association between *growth* in depressive symptoms and conversion to AD. Additionally, steeper increase in depressive symptoms was associated with conversion even in the prodromal stage of the disease (i.e., CN to MCI). Thus,

depressive symptoms may be an early risk factor for disease progression even before the onset of objective cognitive decline.

Apathy also was associated with greater likelihood of progression of disease, consistent with evidence indicating that apathy serves as a risk factor for conversion from MCI to AD (e.g., Palmer et al., 2010; Richard et al., 2012; Ruthirakuhan et al., 2019). The current results indicate that apathy might be a risk factor for progression of cognitive impairment even in the prodromal stage of AD. Similarly, other studies find that apathy in cognitively healthy older adults is associated with cognitive decline (Clarke et al., 2010), higher likelihood of incident MCI (Geda et al., 2014), and development of dementia over the following decade (Bock et al., 2020). Thus, apathy at any stage of the AD disease process, including prior to onset of cognitive symptoms, may signal greater risk for progression of disease.

5.4 Association Between Neural Changes and Progression of Disease

Faster atrophy in the amygdala, ACC, and PCC was associated with greater likelihood of conversion from CN to MCI and from MCI to AD. This finding supports the shared neuropathological model (Geda et al., 2013; Porsteinsson & Antonsdottir, 2015) by establishing a role for neurodegeneration in emotion centers in the brain in predicting faster progression of disease. Prior research has mainly focused on associations between cross-sectional cortical volume in the medial temporal lobes, including the hippocampus and the entorhinal cortex (e.g., Apostolova et al., 2006; Devadand et al., 2007; Mitolo et al., 2019; Yi et al., 2016) and subsequent risk for conversion from MCI to AD. The current results expand on the extant literature by establishing associations between volume loss in the limbic system and subsequent

progression of disease, even before diagnosis of MCI. The current results also focus specifically on atrophy, not cross-sectional volume, of brain structures, allowing for a more direct link between the neurodegenerative process and clinical symptoms. Longitudinal MRI tracking of atrophy in brain structures that support emotion function may represent a clinically useful metric of risk for conversion from MCI to AD.

5.5 Support for Theoretical Models of Neuropsychiatric Symptoms in MCI

As previously noted, findings from the current study provide partial support for the shared neuropathological model of NPS in MCI, which asserts that NPS are noncognitive manifestations of underlying AD-related neurodegeneration. Specifically, as discussed above, there was evidence of faster atrophy in the CI group than the CN group in areas of the brain essential for emotion processing and regulation (i.e., amygdala, ACC, PCC). The current findings of accelerated atrophy in emotion centers of the brain extend prior applications of the shared neuropathological model in AD to the prodromal and MCI stages of the disease (Van Dam et al., 2016).

The shared neuropathological model of NPS inherently assumes that changes in neural structures and circuits precede changes in symptoms of depression and apathy. Results did not demonstrate a pattern of consistent findings along these lines. Whereas amygdala and PCC volume at six months negatively predicted the likelihood of endorsement of apathy at the subsequent timepoint, no other temporal associations were found between neural symptoms and later apathy. Additionally, there was a bidirectional relationship between amygdala volume and depressive symptoms, which may argue for a more complex relationship between neural changes and depressive symptoms than is offered by the shared neuropathological model.

5.6 Limitations

Conclusions from the present study should be interpreted with several limitations in mind. First, there were low levels of endorsement of depressive symptoms and apathy in the sample. Indeed, limited variability in apathy ratings precluded execution of certain planned analyses. There are several potential reasons for low endorsement of depressive symptoms and apathy in the current sample. There is evidence from community samples that NPS may arise before cognitive symptoms in most persons that go on to develop MCI and AD (Wise et al., 2019). However, enrollment criteria for ADNI excluded subjects with depressive symptoms (i.e., GDS > 6), which may have limited the prevalence and variability of NPS in the current sample by excluding persons on the disease spectrum whose first symptoms were neuropsychiatric rather than cognitive. It is also possible that early symptoms of depression and apathy in MCI are subtle and difficult to assess with the abbreviated symptom scales included in ADNI (i.e., GDS-SF, NPI-Q).

Second, the sample is almost entirely White and relatively highly educated. Previous studies have established increased prevalence of AD in Black and Latinx older adults, which may be related to health disparities driven by systemic racism (e.g., Mayeda et al., 2016; Meeker et al., 2021). Results may not generalize to samples with greater racial, ethnic, and socioeconomic diversity given the impact of psychosocial factors on health outcomes and cognitive function. Additionally, sex differences in the associations between neural changes, neuropsychiatric symptoms, and disease progression were not investigated. Sex is a potentially important moderator variable

because some studies have identified sex differences in the prevalence of neuropsychiatric symptoms (e.g., Inamura et al., 2020),.

Third, measurement of depressive symptoms was limited to a brief questionnaire, which did not allow for more granular examination of subtypes of symptoms (e.g., physical vs. cognitive vs. affective). Additionally, apathy was assessed with one item on the NPI-Q, and was rated by research participants' care partners, rather than the research participants themselves. Apathy ratings may thus be more reflective of participants' behavior, rather than the internal experience of reduced motivation or interest.

5.7 Future Directions

The current study identified associations between change in neural markers of emotion dysregulation and change in symptoms of depression and apathy in persons with normal cognition and MCI. An important step for future research will involve testing the aims of the current study in a sample that more accurately reflects the range of NPS found in MCI. Further, it may be useful to investigate the current hypotheses in a sample that includes persons with mild AD at baseline. NPS are more frequently reported as the disease progresses (e.g., Di Iulio et al., 2010; Lyketsos et al., 2002), so including subjects that have progressed farther along the AD disease spectrum may allow for more reliable estimation of associations between NPS and underlying neural changes across the disease process.

The current study focused exclusively on symptoms of depression and apathy, not NPS more generally. Future research is needed to determine whether disruption in emotion centers in the brain is predictive of development of NPS overall, or if different

areas of the brain are associated with development of different symptoms (e.g., anxiety versus agitation).

There were significant associations between amygdala volume and later symptoms of apathy, whereas there was a bidirectional relationship between amygdala volume and depressive symptoms. Further research is needed to determine whether there is a reliable, predictive association between amygdala atrophy and development of depression and apathy. The bidirectional relationship between amygdala volume and depressive symptoms may indicate a more complex feedback loop between amygdala atrophy and development of NPS than is described by the shared neuropathological model. Research into alternative theories of NPS in AD might compliment the current research and advance efforts to determine specific mechanisms of the development of NPS in aMCI.

The long term aim of this line of research is to characterize the etiology and consequences of affective dysregulation in persons with MCI and AD. To this end, it may be important to expand the operationalization of affective dysregulation to include specific behavioral markers, rather than using depression and apathy as proxies for affective dysregulation. Such studies would allow for development of a better understanding of how degeneration of emotion centers in the brain manifests in daily life and by which specific mechanisms these changes lead to observed functional and behavioral difficulties. Clarification of the neurobiology of NPS in aMCI may elucidate why standard psychopharmacological treatments for apathy and depression symptoms are not efficacious (Lyketsos & Miller, 2012), and may identify candidate mechanisms for treatment.

Table 1

Sample Characteristics and Descriptive Statistics

Variable	Baseline CN n = 224 *M* (*SD*) or %	Baseline MCI n = 339 *M* (*SD*) or %	Test Statistic *t* or χ^2
Age	73.46 (6.00)	72.38 (7.28)	1.84
Female	52.7%	44.0%	4.12*
Race			13.26*
White	91.1%	95.0%	
Black	5.8%	1.5%	
Native American	--	0.3%	
Asian/Pacific Islander	0.9%	1.5%	
Multiracial	2.2%	0.9%	
Ethnicity			7.60*
Hispanic/Latino	5.4%	2.1%	
Non-Hispanic/Latino	93.8%	97.9%	
Education	16.63 (2.52)	15.99 (2.78)	2.80**
Baseline CDR	0.65 (0.22)	1.52 (0.89)	28.74***
Baseline MMSE	29.01 (1.21)	27.86 (1.73)	9.13***
Baseline GDS-SF	1.84 (1.13)	2.84 (1.54)	8.77***
Baseline Apathy	2.8%	20.1%	33.84***
Years of follow-up	3.46 (1.95)	2.71 (1.15)	5.20***
% converted	19%	32%	

Note. CDR = Clinical Dementia Rating scale. MMSE = Mini Mental State Exam. GDS = Geriatric Depression Scale Short Form. Apathy scores were dichotomized to reflect presence versus absence of apathy.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 2

Between-Subject Correlations Between Study Variables and Covariates

Variable	1.	2.	3.	4.	5.
1. Age	--				
2. Education	-.07	--			
3. GDS	-.10*	-.07	--		
4. Apathy	-.03	-.07	.26***	--	
5. Conversion	.13**	-.04	.13**	.28***	--

Note. GDS = Geriatric Depression Scale Short Form. Apathy scores were dichotomized to reflect presence versus absence of apathy. Conversion reflects a dichotomous variable indicating whether disease status was stable or progressed over the course of the study. Spearman's ρ is provided for all correlations with Apathy and Conversion.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 3

Parameter Estimates for Parallel Process Models Predicting Longitudinal Associations Between Depressive Symptoms and Neural Markers

	Parameter	Baseline γ (se)	Slope γ (se)
Model 1	GDS	3.67 (0.30)***	0.12 (0.044)**
	Group	-1.70 (0.20)***	0.025 (0.078)
	Age	-0.049 (0.014)***	0.014 (0.005)*
	Education	0.002 (0.035)	-0.029 (0.014)*
	Amygdala Volume	13.41 (0.11)***	-0.17 (0.11)***
	Group	0.86 (0.20)***	0.10 (0.020)***
	Age	-0.10 (0.014)***	-0.005 (0.001)**
	Education	0.088 (0.035)*	0.000 (0.004)
Covariances	GDS Slope*NeurSlope	-0.004 (0.007)	
	GDSInt*GDSSlope	0.044 (0.083)	
	NeurInt*NeurSlope	0.061 (0.020)**	
Model 2	GDS	3.70 (0.11)***	0.12 (0.44)**
	Group	-1.7 (0.20)***	0.027 (0.078)
	Age	-0.049 (0.014)***	0.014 (0.005)*
	Education	0.002 (0.035)	-0.029 (0.014)*
	Caudal ACC Volume	19.17 (0.18)***	-0.17 (0.015)***
	Group	0.013 (0.022)	0.079 (0.026)**
	Age	0.061 (0.055)	-0.003 (0.002)
	Education	0.199 (0.32)	-0.007 (0.005)
Covariances	GDS Slope*NeurSlope	0.011 (0.009)	
	GDSInt*GDSSlope	0.061 (0.082)	
	NeurInt*NeurSlope	-0.143 (0.041)**	
Model 3	GDS	3.70 (0.11)***	0.12 (0.044)**
	Group	-1.70 (0.20)***	0.024 (0.078)
	Age	-0.049 (0.014)***	0.013 (0.005)*

	Education	0.002 (0.035)	-0.029 (0.014)*
	Rostral ACC Volume	23.22 (0.20)***	-0.17 (0.018)***
	Group	-0.46 (0.36)	0.13 (0.031)***
	Age	0.058 (0.025)*	-0.004 (0.002)
	Education	0.15 (0.063)*	-0.001 (0.006)
Covariances	GDS Slope*NeurSlope	0.013 (0.010)	
	GDSInt*GDSSlope	0.058 (0.048)	
	NeurInt*NeurSlope	-0.14 (0.014)*	
Model 4	GDS	3.70 (0.11)***	0.12 (0.44)**
	Group	-1.70 (0.20)***	0.025 (0.078)
	Age	-0.049 (0.014)***	0.014 (0.005)*
	Education	0.002 (0.035)	-0.028 (0.014)*
	PCC Volume	30.09 (0.20)***	-0.039 (0.024)***
	Group	0.47 (0.37)	0.20 (0.043)***
	Age	-0.061 (0.025)*	-0.001 (0.003)
	Education	0.097 (0.063)	-0.007 (0.008)
Covariances	GDS Slope*NeurSlope	-0.006 (0.015)	
	GDSInt*GDSSlope	0.050 (0.083)	
	NeurInt*NeurSlope	-0.010 (0.073)	
Model 5	GDS	3.70 (0.11)***	0.12 (0.44)**
	Group	-1.71 (0.20)***	0.026 (0.078)
	Age	-0.049 (0.014)***	0.013 (0.005)*
	Education	0.002 (0.035)	-0.029 (0.014)*
	DMN Connectivity	9.77 (0.19)***	0.16 (0.10)
	Group	0.15 (0.33)	-0.086 (0.17)
	Age	-0.013 (0.024)	-0.007 (0.015)
	Education	0.064 (0.064)	-0.005 (0.035)
Covariances	GDS Slope*NeurSlope	-0.025 (0.005)	
	GDSInt*GDSSlope	0.059 (0.082)	

NeurInt*NeurSlope	0.074 (0.20)

Note. Age and education were grand mean centered in all models. Group was coded such that intercept values reflect the average for the cognitively impaired group. GDS = Geriatric Depression Scale. GDSSlope = slope of change in GDS scores over time. NeurSlope = slope of change in neural marker over time. GDSInt = mean GDS score at baseline. NeurInt = mean value for neural marker at baseline. ACC = anterior cingulate cortex. PCC = posterior cingulate cortex. DMN = default mode network.
* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 4

Parameter Estimates for Latent Growth Models with Apathy and Neural Markers

Parameter	Amygdala Volume γ (se)	cACC Volume γ (se)	rACC Volume γ (se)	PCC Volume γ (se)	DMN Connectivity γ (se)
Intercept	14.07 (0.17)***	19.072 (0.27)***	22.93 (0.31)***	29.61 (0.31)***	9.92 (0.27)***
Age	-0.10 (0.014)***	-0.014 (0.022)	0.055 (0.025)*	-0.060 (0.025)*	-0.014 (0.024)
Education	0.088 (0.035)*	0.061 (0.055)	0.15 (0.062)*	0.098 (0.063)	0.07 (0.064)
Apathy	-0.84 (0.69)	-1.51 (1.08)	-2.53 (1.23)*	0.29 (1.25)	-0.056 (0.41)
Group	-0.89 (0.22)***	0.13 (0.35)	0.41 (0.39)	0.44 (0.40)	-0.16 (0.36)
ApathyXGroup	0.77 (0.73)	1.44 (1.15)	2.14 (1.30)	-0.13 (1.33)	--
Slope	-0.060 (0.017)***	-0.087 (0.022)***	-0.038 (0.026)	-0.20 (0.035)***	0.084 (0.13)
Age	-0.005 (0.001)***	-0.003 (0.002)	-0.004 (0.002)*	-0.001 (0.003)	-0.007 (0.015)
Education	-0.001 (0.004)	-0.008 (0.005)	-0.002 (0.006)	-0.010 (0.007)	-0.010 (0.034)
Apathy	-0.016 (0.066)	-0.012 (0.085)	-0.026 (0.10)	0.054 (0.14)	0.016 (0.21)
Group	-0.078 (0.022)***	-0.044 (0.028)	-0.10 (0.034)**	-0.13 (0.045)**	0.072 (0.18)
ApathyXGroup	-0.075 (0.071)	-0.11 (0.091)	-0.057 (0.11)	-0.29 (0.15)	--

Note. Age and education were grand mean centered in all models. Group was coded such that intercept values reflect the average for the cognitively impaired group. ApathyXGroup reflects the interaction between the binary apathy variable and group. cACC = caudal anterior cingulate cortex. rACC = rostral anterior cingulate cortex. PCC = posterior cingulate cortex. DMN = default mode network. * $p < .05$. ** $p < .01$. *** $p < .001$.

Table 5

Parameter Estimates for Lagged Predictor and Outcome Models with Depressive Symptoms and Neural Markers

Outcome Variable	Lagged Predictor γ (95% CI)	Lagged Outcome γ (95% CI)
Amygdala Volume	**-1.06 (-1.69 to -0.29)**	**-0.033 (-0.060 to -0.002)**
Caudal ACC Volume	-0.080 (-0.63 to 0.50)	-0.025 (-0.063 to 0.014)
Rostral ACC Volume	-0.25 (-0.15 to 0.67)	-0.014 (-0.060 to 0.038)
PCC Volume	0.17 (-0.062 to 0.44)	-0.030 (-0.073 to 0.008)
DMN Connectivity	**0.25 (0.093 to 0.39)**	-0.033 (-0.33 to 0.21)

Note. ACC = anterior cingulate cortex. PCC = posterior cingulate cortex. DMN = default mode network. Significant pathways are highlighted in bold.

Table 6

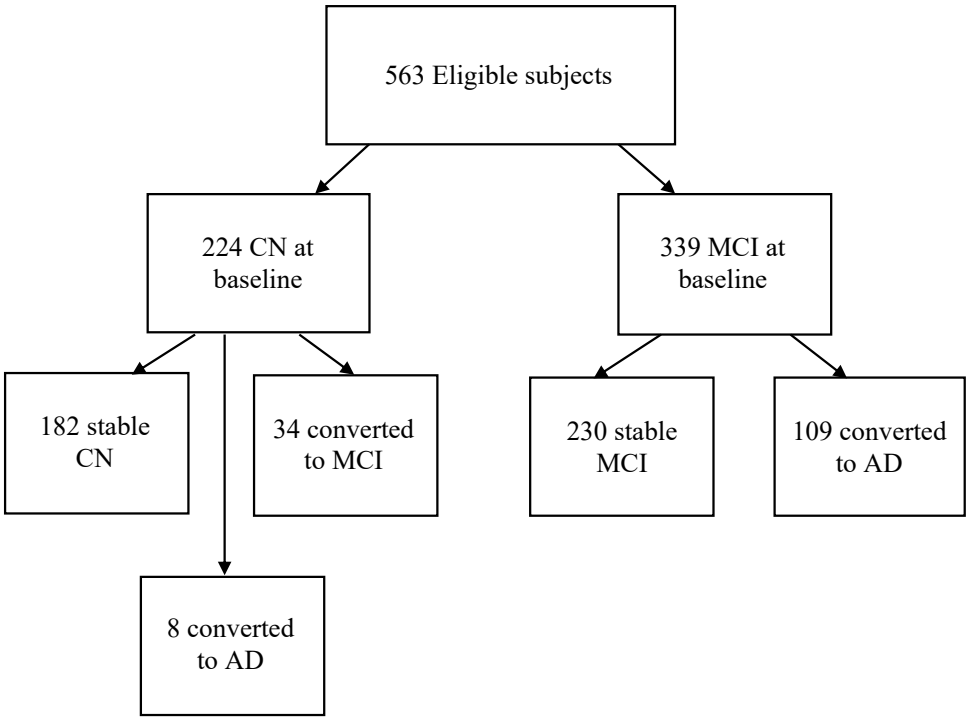
Parameter Estimates for Cross-Lagged Panel Analyses with Apathy and Neural Markers

Parameter	Amygdala Volume γ (se)	cACC Volume γ (se)	rACC Volume γ (se)	PCC Volume γ (se)
Stability Paths				
Ap0 → Ap1	1.09 (0.55)*	0.98 (0.51)$^{+}$	1.03 (0.51)*	0.95 (0.48)$^{+}$
Ap1 → Ap2	0.84 (0.20)***	0.82 (0.19)***	0.81 (0.19)***	0.84 (0.19)***
Ap2 → Ap3	1.33 (0.45)**	1.44 (0.48)**	1.45 (0.46)**	1.32 (0.40)**
Neur0 → Neur1	0.98 (0.020)***	0.97 (0.027)***	0.96 (0.022)***	0.99 (0.023)***
Neur1 → Neur2	1.01 (0.016)***	1.01 (0.027)***	1.01 (0.029)***	0.96 (0.026)***
Neur2 → Neur3	1.00 (0.029)***	0.99 (0.017)***	1.01 (0.027)***	1.07 (0.030)***
Cross-Lagged Paths				
Neur0 → Ap1	-0.38 (0.54)	-0.11 (0.26)	-0.18 (0.26)	0.17 (0.21)
Neur1 → Ap2	-1.17 (0.46)*	-0.61 (0.33)$^{+}$	-0.63 (0.33)$^{+}$	-0.58 (0.26)*
Neur2 → Ap3	-1.47 (1.31)	1.01 (0.78)	0.84 (0.67)	-0.42 (0.47)
Ap0 → Neur1	-0.025 (0.033)	-0.030 (0.029)	0.002 (0.038)	0.023 (0.036)
Ap1 → Neur2	-0.008 (0.008)	-0.018 (0.010)$^{+}$	-0.026 (0.017)	-0.005 (0.014)
Ap2 → Neur3	-0.010 (0.008)	0.004 (0.011)	-0.001 (0.012)	-0.011 (0.010)
Concurrent Covariance				
Ap0*Neur0	0.019 (0.016)	0.012 (0.013)	0.004 (0.011)	0.004 (0.012)
Ap1*Neur1	0.008 (0.011)	0.008 (0.010)	0.010 (0.015)	-0.017 (0.014)
Ap2*Neur2	-0.015 (0.011)	0.001 (0.013)	-0.036 (0.019)$^{+}$	0.002 (0.016)
Ap3*Neur3	-0.006 (0.031)	-0.054 (0.041)	-0.096 (0.046)*	-0.036 (0.048)

Note. All models controlled for patient age and education. cACC = caudal anterior cingulate cortex. rACC = rostral anterior cingulate cortex. PCC = posterior cingulate cortex. Ap = Apathy score. Neur = neural marker.
$^{+}$ p < .10. * p < .05. ** p < .01. *** p < .001.

Figure 1

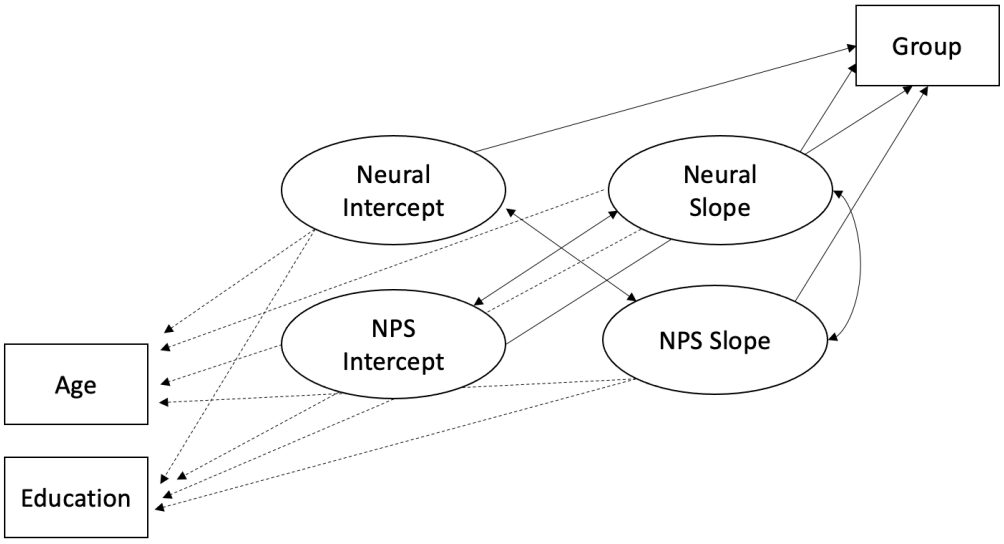
Flowchart of Subject Groups



Note. CN = Cognitively normal. MCI = mild cognitive impairment. AD = Alzheimer's disease.

Figure 2

Conceptual Model for Parallel Process Models with Depressive Symptoms and Neural Markers



Note. Solid lines represent parameter estimates for pathways of interest; dotted lines reflect parameter estimates for covariates in the model. NPS = neuropsychiatric symptom. Group represents cognitive normal subjects versus those that developed cognitive impairment at some point in the study.

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