Received: 13 February 2018 | Accepted: 22 July 2018

DOI: 10.1002/gps.4963

RESEARCH ARTICLE

WILEY International Journal of Geriatric Psychiatry

# Examining differences in neuropsychiatric symptom factor trajectories in empirically derived mild cognitive impairment subtypes

Alyssa N. De Vito | Matthew Calamia | Daniel S. Weitzner | John P.K. Bernstein | for the Alzheimer's Disease Neuroimaging Initiative

Department of Psychology, Louisiana State University, Baton Rouge, Louisiana

**Correspondence**
Alyssa De Vito, Department of Psychology, Louisiana State University, 236 Audubon Hall, Baton Rouge, LA 70803, USA.
Email: adevit1@lsu.edu

**Objective:** The aim of this study was to examine neuropsychiatric symptom (NPS) factor severity progression over time in empirically derived (ED) mild cognitive impairment (MCI) subtypes.

**Methods:** Participants in the Alzheimer's Disease Neuroimaging Initiative study diagnosed with MCI by Alzheimer's Disease Neuroimaging Initiative protocol using conventional clinical (CC) criteria (n = 788) were reclassified using cluster analysis as amnestic, dysnomic, dysexecutive MCI, or cluster-derived normal (CC-Normal) using empirical criteria. Cognitively normal (CN) participants (n = 207) were also identified. The Neuropsychiatric Inventory-Questionnaire (NPI-Q) was administered from baseline through 48-month follow-up. Exploratory factor analysis was completed to determine the NPI-Q factor structure at 6-month follow-up. Multilevel modeling was used to determine NPI-Q symptom severity factor and apathy symptom progression over time by cognitive subtype.

**Results:** The exploratory factor analysis revealed that the NPI-Q consisted of 2 factors: hyperactivity/agitation and mood symptoms. Using clinical and empirical criteria, all MCI groups were identified as having more severe hyperactivity/agitation symptoms than CN participants. However, only the amnestic MCI group identified using empirical criteria showed an increase in symptom severity over time relative to CN participants. Mood factor and apathy symptoms were found to be more severe in dysexecutive and amnestic groups in both models. Similarly, both models identified a significant worsening of mood and apathy symptoms over time for dysexecutive and amnestic groups relative to CN participants.

**Conclusions:** This study provides further support that empirical criteria aid in examining the progression of clinical characteristics associated with MCI. Further, it helps to identify which MCI subtypes may be at higher risk for NPS progression.

KEYWORDS

Alzheimer's disease, dementia, mild cognitive impairment, neuropsychiatric symptoms

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

  

## 1 | INTRODUCTION

Alzheimer's disease (AD) is a growing public health problem, with an estimated 5.5 million people living with the disease in 2017 in the United States. By 2050, these rates are projected to increase to approximately 16 million people in the United States.[1] There is substantial biological and clinical evidence that neuropathological processes begin years before functional decline is evident.[2] Therefore, the understanding and identification of prodromal elements of AD is crucial for future disease intervention.

The most widely studied prodromal state of progressive dementias such as AD is mild cognitive impairment (MCI), a condition that is conceptualized as the transition between normal cognition and dementia. Patients with MCI have subjective and/or objective neuropsychological evidence of mild memory complaints in the absence of significant functional decline.[3] In recent years, a series of studies have highlighted the need for empirically derived MCI diagnosis because of increased susceptibility of false positive errors when utilizing conventional MCI criteria.[3,4] Conventional criteria used to diagnose MCI utilizes cognitive screening measures (e.g., MMSE), limited neuropsychological assessment (e.g., 1 memory subtest), and clinical judgement[5] whereas empirical criteria relies heavily on broader neuropsychological assessment (e.g., using several tests to measure across cognitive domains) as well as clinical judgment. Research using empirical criteria has identified several subtypes of MCI: individuals with a primary impairment in memory (amnestic) or a primary impairment in other cognitive domains (nonamnestic) such as a primary impairment in language (dysnomic), a primary impairment in executive function (dysexecutive), as well as a subtype with impairments in more than 1 domain (multidomain MCI).[6,7]

The identification of these subtypes has been shown to improve diagnostic precision of MCI[3] and has clarified relationships with prodromal biomarkers of AD as well as identified differing disease trajectories among subtypes.[6,8] Further, a study by Thomas and coworkers (2017) identified differing functional status trajectories across empirically derived MCI subtypes, such that dysexecutive individuals experienced steeper rates of functional decline over time compared to dysnomic or amnestic groups.[9] While many studies have examined biomarkers in empirically derived MCI subtypes, prodromal clinical markers such as neuropsychiatric symptoms (NPS) have not been yet examined in the context of these subtypes.

Neuropsychiatric symptoms are psychiatric or behavioral symptoms of dementia that often precede significant cognitive decline.[10] Neuropsychiatric symptoms are prevalent in both early and later stages of progressive dementias with approximately 50% of individuals with MCI experiencing at least 1 NPS.[11] The presence of NPS, even of mild severity, is linked with accelerated and higher rates of progression from MCI to dementia,[10] increased functional impairment,[12] higher need for institutionalized care,[13] poorer quality of life,[14] substantial neuropathological burden,[15,16] and increased caregiver burden.[17]

Investigations into the role that NPS play in MCI as well as risk for conversion to AD have been limited. The majority of studies use conventional rather than empirical diagnostic criteria,[18,19] examine a single NPS (e.g., anxiety), or examine the overall number or severity of NPS.[2] Previous research suggests that clinically derived subtypes of MCI may have differing NPS profiles, although the literature is mixed regarding these relationships.[18,20] Previous work suggests that individuals with amnestic MCI may be more likely to develop NPS, have more severe NPS trajectories, and be more likely to progress to dementia than those with nonamnestic MCI.[20,21] However, other studies found few associations between amnestic MCI and NPS.[18] Prodromal differences in NPS profiles may result from early neurodegeneration that is not yet detectable by screening measures.

Recent neuroimaging research provides support for differing NPS profiles by linking certain NPS to brain regions that are commonly affected in specific MCI subtypes. For example, Pa and coworkers (2009) found that individuals with left prefrontal atrophy, a region impaired in those with dysexecutive MCI, were more likely to experience behavioral (e.g., disinhibition) and emotional regulation problems.[22]

This study proposes to build upon previous work by examining the presence and progression in severity of NPS factors in the context of empirically derived subtypes of MCI. Examining NPS symptom factors rather than specific symptoms is likely to lead to increased ease in identifying associations between symptoms and trajectories as well as making intervention more feasible.[23,24] Given that NPS often serve as prodromal warning signs of cognitive decline, a better understanding of how these symptoms operate in MCI is likely to facilitate potential for earlier detection and intervention for both cognitive and psychiatric symptoms.[10]

**Key points**

- Empirically derived mild cognitive impairment (MCI) subtypes have different neuropsychiatric symptom factor trajectories.
- Amnestic MCI participants experienced more severe agitation/hyperactivity symptoms compared to other MCI subtypes.
- Amnestic and dysexecutive MCI participants experienced more severe mood and apathy symptoms over time compared to dysnomic MCI subtypes.

## 2 | METHODS

### 2.1 | Participants

The present study was approved by the Louisiana State University institutional review board. The study included 788 MCI participants and 207 cognitively normal (CN) participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Criteria for ADNI eligibility and diagnostic classifications are described at http://www.adni-info.org/Scientists/ADNIGrant/ProtocolSummary.aspx. All participants were 55 to 91 years old, had a modified Hachinski score $\leq$4, and had an informant whom was able to provide an evaluation of functioning. See Table 1 for demographic information. The CN group included individuals who remained cognitively normal throughout their participation in ADNI.

**TABLE 1** Sample demographics

| | Age, years M (SD) | Gender, % Female | Education, years M (SD) | Symptom Severity M (SD) |
|---|---|---|---|---|
| Conventional criteria | | | | |
| Cognitively normal | 76.3 (5.4) | 47.0% | 16.0 (2.8) | 0.62 (1.3) |
| Cluster-derived normal | 74.4 (8.2) | 39.1% | 16.3 (2.6) | 1.89 (2.6) |
| Dysexecutive MCI | 74.8 (7.1) | 38.3% | 14.5 (3.5) | 2.52 (3.3) |
| Amnestic MCI | 73.2 (7.0) | 35.6% | 15.9 (2.8) | 2.45 (2.9) |
| Neuropsychological criteria | | | | |
| Cognitively normal | 76.3 (5.4) | 47.0% | 16.0 (2.8) | 0.62 (1.3) |
| Dysexecutive/mixed MCI | 75.1 (7.3) | 38.9% | 14.4 (3.7) | 2.65 (3.6) |
| Dysnomic MCI | 74.0 (6.0) | 36.1% | 16.2 (2.7) | 1.97 (2.5) |
| Amnestic MCI | 73.6 (7.1) | 39.0% | 15.9 (2.8) | 2.37 (2.9) |

## 3 | MEASURES

### 3.1 | Neuropsychiatric Inventory-Questionnaire

The NPI-Q[25] is a brief 12-item, informant-based questionnaire that assesses psychopathology that commonly occurs in progressive cognitive decline. In the ADNI study, the NPI-Q is administered at baseline as well as every 6 months during follow-up visits.

### 3.2 | Neuropsychological testing

Following baseline ADNI diagnosis, participants completed a neuropsychological test battery at yearly follow-up. The battery included tests of episodic memory (Rey Auditory Verbal Learning Test),[26] language (Category Fluency Test-Animals[27]; Boston Naming Test (30 items),[28] and attention/executive functioning (Trail-Making Test Parts A and B).[29]

### 3.3 | Clinical diagnostic classification

Mild cognitive impairment was diagnosed by ADNI using the following conventional clinical (CC) criteria: (1) self-reported, informant-reported, and/or clinician-reported memory problems; (2) performing below an education-adjusted normative cutoff score on delayed recall of story A of the WMS-R Logical Memory Test; (3) global clinical dementia rating score of 0.5; and (4) general cognitive and functional performance such that dementia could not be diagnosed at baseline.[30]

### 3.4 | Neuropsychological diagnostic classification

Empirically derived (ED) diagnostic classification was determined by the procedure outlined by Bondi and colleagues.[6] All ADNI CN and MCI participants were reclassified using the Jak/Bondi neuropsychological-based method applied to their baseline data. Five neuropsychological subtests from ADNI were chosen because of their well-established use in the assessment of MCI and consistent administration across all 4 ADNI study periods.[6] These measures were not used in determining ADNI cognitive status diagnosis at initial screening as only the WMS-IV Logical Memory subtest was used per ADNI study procedure. Each measure was converted to an age-corrected *z*-score using widely accepted normative data as outlined by Bondi and colleagues[6]: Mayo Older Americans Normative Study[31] for the Rey Auditory Verbal Learning Test and National Alzheimer's Coordinating Center normative[27,32] for the remaining neuropsychological measures. Participants were considered to have MCI if any of the following criteria were met: (1) They performed >1 SD below the age-corrected normative mean or on both scores within at least 1 cognitive domain (i.e., memory, language, or attention/executive function) and (2) performed >1 SD below the age-corrected normative mean, in each of the 3 cognitive domains.[6]

## 4 | STATISTICAL ANALYSES

### 4.1 | Descriptive statistics

Differences in baseline demographic characteristics between groups were evaluated using chi-square tests for categorical variables. Analysis of variance (ANOVA) was used to examine differences between groups for continuous demographic and neuropsychological variables.

### 4.2 | Cluster analysis

Cluster analytic methodology outlined in Bondi and colleagues was used to determine MCI subtype.[6] In the first hierarchical cluster analysis, individuals diagnosed as MCI using CC criteria were completed. In previous studies as well as the current study, the first cluster analysis aids in identifying individuals who have been diagnosed with MCI, but who are cognitively normal by neuropsychological standards.[6] A second hierarchical analysis was conducted using ED criteria, which has been used in previous studies to identify an additional ED-MCI cluster.[6] Ward's method was used in both analyses to calculate the distance between each cluster (squared Euclidean distance) and merge clusters together that produced the smallest increase in overall distances within clusters.

### 4.3 | Factor analysis

The factor structure of the NPI-Q was evaluated using exploratory factor analysis (EFA) with an oblique rotation, as significant correlation among the factors was expected (Mplus, 7.2).[33] A robust estimator appropriate for ordinal item responses was used (WLSMV) as there are only 4 response categories on the NPI-Q severity scale.[34] Two questions (delusions and hallucinations) were excluded from analyses

because of low base rate in the sample. Based on the findings of the factor analysis, composites were calculated by summing the NPI-Q severity scores. For the current study, the baseline assessment was excluded from analysis because of a lack of variability in symptom severity[35] and because fewer participants were given the NPI-Q at baseline compared to at their 6-month follow-up visit. Therefore, by beginning analysis with the 6-month visit rather than at baseline, this allowed for a larger sample size.

### 4.4 | Multilevel modeling

Multilevel modeling was used to determine whether there were differences in NPI-Q symptom severity composite scores over time by group. The visit variable included 8 time points that spanned over 4 years. The first analysis using CC criteria included 4 groups: a cognitively normal group (CN), a cluster-derived normal group (CC-Normal), a dysexecutive MCI group (CC-EF), and an amnestic MCI (CC-Amnestic) group. The second analysis using ED criteria included 4 groups: a cognitively normal group (CN), a dysexecutive MCI group (ED-EF), a dysnomic MCI group (ED-Lang), and an amnestic MCI group (ED-Amnestic). In both analyses, CN participants were used as the reference group. Age and education were included as covariates as they were found to differ between groups. The intercept was included as a random effect in the model.

## 5 | RESULTS

### 5.1 | Cluster analysis

Cluster analysis of 788 participants diagnosed with MCI using CC criteria resulted in 3 subtypes consistent with previous studies 6. 326 participants who performed within the normal range on all neuropsychological measures were considered to be cluster-derived normal (CC-Normal). 336 individuals who were primarily impaired on memory measures were considered to be amnestic MCI (CC-Amnestic). 126 participants who performed most poorly on attention/executive function measures and had mildly impaired performance on memory and language were considered to have dysexecutive/mixed MCI (CC-EF). At baseline, significant differences were found between groups on age, education, and overall NPI-Q symptom severity, but not gender.

The second hierarchical cluster analysis using the 462 individuals diagnosed with MCI using the ED criteria resulted in 3 subtypes.[6] 300 individuals who were primarily impaired on memory measures were considered to be amnestic MCI (ED-Amnestic). 100 participants who performed most poorly on attention/executive function measures and had mildly impaired performance on memory and language were considered to have dysexecutive/mixed MCI (ED-EF). 62 participants who had primary impairment on language measures and mild impairments in other domains were classified as dysnomic (ED-Lang). At baseline, significant differences were found between groups on age, education, and overall NPI symptom severity, but not gender. See Table 1 for demographic descriptive statistics.

### 5.2 | Factor analysis

The results of the EFA are shown in Table 2. The EFA revealed a 2-factor solution: the first factor consisted of symptoms that are related to "agitation/hyperactivity" and the second factor consisted of symptoms related to "mood problems." Apathy was not included in either factor because of high cross-loading on both factors; however, a follow-up analysis was conducted to examine differing trajectories of apathy severity amongst MCI subtypes.

### 5.3 | Multilevel modeling

In both the CC and ED models that examined agitation/hyperactivity symptoms, there were main effects for group, such that the CC-Normal, CC-EF, ED-EF, CC-Amnestic, and ED-Amnestic groups exhibited more symptoms than CN participants at baseline. There were no main effects of visit, age, or education. In the model using CC criteria, no group by visit interaction was significant. However, in the ED criteria model, a group by visit interaction was observed for the ED-Amnestic group, which suggests that ED-Amnestic individuals experienced more severe agitation/hyperactivity over time. See Table 3 for a summary of agitation/hyperactivity model results.

With respect to mood symptoms (see Table 4), there were no differences in the models utilizing CC or ED criteria, which demonstrated group main effects for CC-Normal, CC-EF, ED-EF, CC-Amnestic, and ED-Amnestic groups at baseline. These results indicate that these individuals experience more severe mood symptoms than CN participants. There were no main effects of visit, age, or education. Group by visit interactions were observed for CC-EF, ED-EF, CC-Amnestic, and ED-Amnestic groups, but not for ED-Lang participants. This indicates that regardless of criteria, dysexecutive and amnestic groups, but not ED-Lang individuals, experienced more severe mood problems over time.

Follow-up analyses examining the trajectory of apathy symptoms among differing MCI subtypes using CC criteria revealed that CC-Normal, CC-Amnestic, and CC-EF participants experienced more apathy symptoms at baseline when compared to CN participants. However, group by visit interactions were only observed for CC-Amnestic and CC-EF groups, indicating that these groups experience more apathy symptoms over time. The model utilizing ED criteria demonstrated that all ED-MCI groups experienced more severe apathy symptoms at baseline compared to CN participants. Similar to CC findings, group

**TABLE 2** Factor loadings of NPI-Q scores at the 6-month visit

| Symptom | Agitation/Hyperactivity | Mood Problems |
|---|---|---|
| Agitation/aggression | **.67** | .24 |
| Dysphoria/depression | −.01 | **.76** |
| Anxiety | .22 | **.53** |
| Euphoria/elation | **.71** | −.03 |
| Apathy/indifference | **.40** | .34 |
| Disinhibition | **.80** | .00 |
| Irritability/lability | **.59** | .25 |
| Aberrant motor | **.56** | −.03 |
| Nighttime behavior | .07 | **.55** |
| Appetite/eating | .00 | **.52** |

Bold indicates factor loading of .4 or greater.

**TABLE 3** Estimates and effect sizes of variables in the agitation/hyperactivity model

| | Estimate | SE | *t* |
|---|---|---|---|
| Conventional criteria | | | |
| Intercept | .49 | .46 | 1.06 |
| Demographic variables | | | |
| Age | .00 | .01 | −.51 |
| Education | .00 | .01 | .32 |
| Visit | .01 | .02 | .69 |
| Group main effect | | | |
| Cluster-derived normal** | .38 | .13 | 3.02 |
| Dysexecutive MCI*** | .80 | .17 | 4.87 |
| Amnestic MCI*** | .72 | .13 | 5.55 |
| Group × visit | | | |
| Cluster-derived normal × visit | .03 | .24 | 1.08 |
| Dysexecutive MCI × visit | .02 | .03 | .49 |
| Amnestic MCI × visit | .04 | .03 | 1.43 |
| Neuropsychological criteria | | | |
| Intercept | .57 | .46 | 1.22 |
| Demographic variables | | | |
| Age | .00 | .00 | −.60 |
| Education | .00 | .01 | .16 |
| Visit | .01 | .02 | .70 |
| Group main effect | | | |
| Dysexecutive MCI*** | .80 | .17 | 4.58 |
| Dysnomic MCI*** | .47 | .13 | 3.65 |
| Amnestic MCI*** | .63 | .13 | 4.99 |
| Group × visit | | | |
| Dysexecutive MCI × visit | .02 | .03 | .50 |
| Dysnomic MCI × visit | .01 | .02 | .31 |
| Amnestic MCI × visit* | .05 | .02 | 2.01 |

Abbreviations: SE, standard error; MCI, mild cognitive impairment.

*$P < .05$,

**$P < .01$,

***$P < .001$.

**TABLE 4** Estimates and effect sizes of variables in the mood model

| | Estimate | SE | *t* |
|---|---|---|---|
| Conventional criteria | | | |
| Intercept | .50 | .44 | 1.14 |
| Demographic variables | | | |
| Age | .00 | .01 | −.23 |
| Education | .00 | .01 | .18 |
| Visit | .02 | .02 | .79 |
| Group main effect | | | |
| Cluster-derived normal** | .40 | .13 | 3.31 |
| Dysexecutive MCI*** | .63 | .16 | 3.93 |
| Amnestic MCI*** | .57 | .13 | 4.52 |
| Group × visit | | | |
| Cluster-derived normal × visit | .02 | .03 | .57 |
| Dysexecutive MCI × visit* | .08 | .03 | 2.07 |
| Amnestic MCI × visit** | .09 | .03 | 3.36 |
| Neuropsychological criteria | | | |
| Intercept | .61 | .44 | 1.40 |
| Demographic variables | | | |
| Age | .00 | .01 | −.44 |
| Education | .00 | .01 | .01 |
| Visit | .02 | .02 | .82 |
| Group main effect | | | |
| Dysexecutive MCI*** | .66 | .17 | 3.86 |
| Dysnomic MCI*** | .44 | .13 | 3.51 |
| Amnestic MCI*** | .54 | .13 | 4.29 |
| Group × visit | | | |
| Dysexecutive MCI × visit* | .07 | .04 | 2.00 |
| Dysnomic MCI × visit | .02 | .03 | .74 |
| Amnestic MCI × visit** | .08 | .03 | 2.88 |

Abbreviations: SE, standard error; MCI, mild cognitive impairment.

*$P < .05$,

**$P < .01$,

***$P < .001$.

by visit interactions were revealed for ED-Amnestic and ED-EF groups, indicating that these groups experience more apathy symptoms over time. The group by visit interaction was not observed in the ED-Lang group. See Table 5 for results.

## 6 | DISCUSSION

The current study provides further support that NPS differ in their reported severity level over time in different MCI subtypes. The current study used both the CC ADNI criteria as well as ED criteria because of findings of increased false positive error rates when utilizing CC criteria.[4,36] Cluster analyses using an updated database with additional participants identified similar groups as in prior analyses of ADNI data.[6]

To identify NPS factors, an EFA was conducted, in which items loaded on 2 factors: an agitation/hyperactivity factor and a mood problems factor. These findings are similar to results found in other studies.[24,37] Other studies have identified a "psychosis" factor,[24] but because of a low base rate in the current sample, this study did not identify a psychosis factor. Apathy demonstrated high cross-loadings on both factors. This is consistent with prior work in patients with dementia showing that apathy is not consistently related to 1 set of NPS.[38] Because of research suggesting its importance as a feature of dementia, apathy was analyzed separately.[39] In the current study, all CC- and ED-MCI participants displayed increased symptoms of apathy compared to CN participants. However, only the CC-Amnestic, CC-EF, ED-Amnestic, and ED-EF groups experienced these increased symptoms over time. These results are in line with previous research identifying increased levels of apathy in those at risk for dementia.[40,41]

Further, all MCI participants displayed more agitation/hyperactivity and mood symptoms at baseline compared to CN participants. This finding was consistent regardless of whether CC criteria or ED criteria were used. CC criteria and ED criteria also both identified the dysexecutive and amnestic groups as experiencing more severe mood symptoms than CN participants over time. However, only the ED criteria identified that the amnestic group experienced more severe agitation/hyperactivity symptoms over time, whereas using CC criteria did not. This finding suggests that initial classification with the CC criteria may

**TABLE 5** Estimates and effect sizes of variables in the apathy symptom model

| | Estimate | SE | *t* |
|---|---|---|---|
| Conventional criteria | | | |
| Intercept | .00 | .17 | .01 |
| Demographic variables | | | |
| Age | .00 | .00 | .09 |
| Education | | | |
| Visit | .01 | .01 | .64 |
| Group main effect | | | |
| Cluster-derived normal* | .12 | .53 | 2.36 |
| Dysexecutive MCI** | .14 | .07 | 2.16 |
| Amnestic MCI*** | .23 | .05 | 4.22 |
| Group × visit | | | |
| Cluster-derived normal × visit | .01 | .01 | .53 |
| Dysexecutive MCI × visit*** | .06 | .01 | 3.97 |
| Amnestic MCI × visit** | .03 | .01 | 2.39 |
| Neuropsychological criteria | | | |
| Intercept | .33 | .23 | .14 |
| Demographic variables | | | |
| Age | −.00 | .00 | −1.40 |
| Education | −.00 | .01 | −35 |
| Visit | .01 | .01 | .42 |
| Group main effect | | | |
| Dysexecutive MCI* | .14 | .07 | 1.93 |
| Dysnomic MCI*** | .29 | .09 | 3.24 |
| Amnestic MCI*** | .21 | .06 | 3.59 |
| Group × visit | | | |
| Dysexecutive MCI × visit*** | .06 | .02 | 3.76 |
| Dysnomic MCI × visit | −.00 | .02 | −.32 |
| Amnestic MCI × visit** | .03 | .01 | 2.75 |

SE, standard error; MCI, mild cognitive impairment

*$P < .05$,

**$P < .01$,

***$P < .001$.

not be sensitive enough to identify changes in these symptoms over time. Neuropsychiatric symptoms (e.g., agitation) are clinically important for several reasons including their association with increased mortality and faster rate of decline in patients with AD.[42] Although symptom severity did not differentially increase over time compared to other groups, baseline symptom severity of agitation and aggression was highest in the ED-EF group. This is consistent with research showing that atrophy of frontal regions of the brain is associated with increased symptoms of agitation[37] and this is crucial because individuals diagnosed with dysexecutive MCI demonstrate atrophy in frontal regions of the brain.[22]

Regarding mood symptoms, there were no differences in model prediction as both the CC and ED criteria models demonstrated that amnestic and dysexecutive individuals experienced more severe symptoms over time. This finding is consistent with research demonstrating that individuals of different subtypes of MCI[43] frequently endorse depressive symptomatology.

In the current study, the CC-Normal group exhibited increased agitation/hyperactivity symptoms and mood symptoms compared to CN participants. However, this group did not show significant increases in either agitation/hyperactivity or mood symptoms over time. It is possible that the CC-Normal group may be classified in other studies as individuals with subjective cognitive decline (SCD). Individuals experiencing NPS, such as anxiety or depression, are more likely to report SCD, even when not displaying objective cognitive impairments.[44] Despite demonstrating a lack of impairment during initial testing, SCD has been shown to be associated with future cognitive decline.[45] Therefore, individuals reporting SCD warrant follow-up testing to monitor for potential future decline in objective cognitive performance. Previous research utilizing the ADNI database has found that individuals reporting SCD have been shown to have to have fewer CSF biomarkers for AD and were less likely to convert to AD than the ED MCI subtypes in a prior study.[3]

Alternatively, the elevated symptoms in this group at baseline may represent 1 reason for potential misdiagnosis of MCI given their association with objective cognitive performance and subjective cognitive complaints. Neuropsychiatric symptoms, such as anxiety or depression, are associated with a decline in memory performance in healthy functional older adults[15,46] as well as reduced processing speed.[47,48] One CC criteria for MCI is subjective cognitive complaints, and research suggests that subjective cognitive complaints may be related to depressive symptoms.[44]

Overall, accurate diagnosis and identification of NPS, and how they change over time, has the potential for numerous short- and long-term health benefits. The current study has demonstrated that use of ED criteria predicted the onset of more severe agitation/hyperactivity symptoms over time in amnestic MCI individuals. Through the use of the ED criteria, diagnoses will become more accurate, and new treatment interventions can be established. Given that different NPS are experienced by individuals in the different MCI subtypes, different treatments may be more beneficial for 1 subtype of MCI as compared to the others. For example, nonpharmacological interventions tailored for individuals with dementia have demonstrated effectiveness in reducing symptoms such as agitation and depression. Therefore, identifying NPS profiles within ED subtypes of MCI has implications for diagnostic clarity and treatment effectiveness.

## 7 | LIMITATIONS

The ADNI database provides an excellent opportunity to study longitudinal relationships among variables related to cognitive decline in potential neurodegenerative processes. The benefits of utilizing this database include a large sample size consisting of clinical and nonclinical populations. However, there are some limitations to the current study, including those associated with analyzing precollected data such as sample collected, study methodology, and alterations to protocols.[49,50]

Previous research suggests that NPS prevalence, severity, and trajectories may differ between types of dementia (e.g., AD type vs. frontotemporal dementia). Given that ADNI aims to recruit participants that are on the trajectory for or have AD-type dementia, this limits the generalizability of these findings to individuals with AD dementia.[51] Further, ADNI protocol requires exclusion of participants with more severe NPS symptoms (e.g., psychosis) at baseline. Therefore, this may help to explain why a psychosis factor was not identified in the current study, but has been identified in previous research.

Due to ADNI's use of CC criteria which relies heavily on the presence of memory impairment to diagnose MCI, individuals who have presentations consistent with nonamnestic MCI may not have been included in the initial sample. Further, individuals reclassified with ED criteria (e.g., ED-Lang) show primary impairment in 1 domain (e.g., language), but may also demonstrate memory impairments. Therefore, these individuals may represent a MCI subtype described in other studies as "MCI, amnestic, multidomain."[52] Although individuals with nonamnestic MCI presentation have been described, the prevalence rates of these MCI subtypes are not clear.

Regarding limitations related to methodology, given that fewer participants were administered the NPI-Q at baseline than at their 6-month follow up, analysis of the NPI-Q items began at the 6-month follow-up. Therefore, symptoms prior to the onset of cognitive testing are not known. Additionally, although other research has used the NPI-Q to measure NPS in individuals with MCI, it was developed to assess NPS in individuals with dementia.[53] Therefore, the utilization of the NPI-Q with a population that may not have symptoms severe enough to warrant a diagnosis of dementia may be inappropriate. Future studies should examine relationships between ED-MCI subtypes and NPS severity and progression using measures that may be more appropriate for the population such as the Mild Behavior Checklist (MBI-C).[54] Lastly, because of its cross-loading on both symptom factors, apathy was analyzed separately, rather than being included in the symptoms factors.

## 8 | CONCLUSION

The current study examined the associations among ED-MCI subtypes and NPS factors. The current study extends prior work on MCI subtypes derived in ADNI based on both CC and ED criteria. Utilizing ED criteria has previously identified differences in MCI subtypes in their association with biomarkers of pathological aging and associations with functional impairment over time. In the current study, differences were observed both in baseline NPS and change over time across subtype. This highlights the utility of examining ED-MCI subtypes when studying NPS in older adults with cognitive decline. These differences may partially explain variability across NPS prevalence rates in studies which define MCI in varying ways and often include participants with different patterns of cognitive deficits.

### ACKNOWLEDGEMENTS

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). Alzheimer's Disease Neuroimaging Initiative is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. Alzheimer's Disease Neuroimaging Initiative data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

### ORCID

*Alyssa N. De Vito* http://orcid.org/0000-0002-4078-3869
*Matthew Calamia* http://orcid.org/0000-0002-7252-7181

### REFERENCES

1. Association As. 2017 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2017;13(4):325-373.
2. Rosenberg PB, Mielke MM, Appleby BS, Oh ES, Geda YE, Lyketsos CG. The association of neuropsychiatric symptoms in MCI with incident dementia and Alzheimer disease. *Am J Geriatr Psychiatry*. 2013;21(7):685-695.
3. Edmonds EC, Delano-Wood L, Galasko DR, Salmon DP, Bondi MW. Subtle cognitive decline and biomarker staging in preclinical Alzheimer's disease. *J Alzheimers Dis*. 2015;47(1):231-242.
4. Jak AJ, Bondi MW, Delano-Wood L, et al. Quantification of five neuropsychological approaches to defining mild cognitive impairment. *Am J Geriatr Psychiatry*. 2009;17(5):368-375.
5. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999;56(3):303-308.
6. Bondi MW, Edmonds EC, Jak AJ, et al. Neuropsychological criteria for mild cognitive impairment improves diagnostic precision, biomarker associations, and progression rates. *J Alzheimers Dis*. 2014;42(1):275-289.
7. Saunders NL, Summers MJ. Longitudinal deficits to attention, executive, and working memory in subtypes of mild cognitive impairment. *Neuropsychology*. 2011;25(2):237-248.
8. Bangen KJ, Clark AL, Werhane M, et al. Cortical amyloid burden differences across empirically-derived mild cognitive impairment subtypes and interaction with APOE ε4 genotype. *J Alzheimers Dis*. 2016;52(3):849-861.
9. Thomas KR, Edmonds EC, Delano-Wood L, Bondi MW. Longitudinal trajectories of informant-reported daily functioning in empirically defined subtypes of mild cognitive impairment. *J Int Neuropsychol Soc*. 2017;23(6):521-527.
10. Gallagher D, Fischer CE, Iaboni A. Neuropsychiatric symptoms in mild cognitive impairment: an update on prevalence, mechanisms, and clinical significance. *Can J Psychiatry*. 2017;62(3):161-169.
11. Geda YE, Roberts RO, Knopman DS, et al. Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: population-based study. *Arch Gen Psychiatry*. 2008;65(10):1193-1198.
12. Ismail Z, Smith EE, Geda Y, et al. Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. *Alzheimers Dement*. 2016;12(2):195-202.
13. Selbæk G, Engedal K, Bergh S. The prevalence and course of neuropsychiatric symptoms in nursing home patients with dementia: a systematic review. *J Am Med Dir Assoc*. 2013;14(3):161-169.

14. Karttunen K, Karppi P, Hiltunen A, et al. Neuropsychiatric symptoms and quality of life in patients with very mild and mild Alzheimer's disease. *Int J Geriatr Psychiatry*. 2011;26(5):473-482.
15. Pietrzak RH, Maruff P, Woodward M, et al. Mild worry symptoms predict decline in learning and memory in healthy older adults: a 2-year prospective cohort study. *Am J Geriatr Psychiatry*. 2012;20(3):266-275.
16. Delano-Wood L, Bondi MW, Sacco J, et al. Heterogeneity in mild cognitive impairment: differences in neuropsychological profile and associated white matter lesion pathology. *J Int Neuropsychol Soc*. 2009;15(6):906-914.
17. Chen CT, Chang C-C, Chang W-N, et al. Neuropsychiatric symptoms in Alzheimer's disease: associations with caregiver burden and treatment outcomes. *QJM: Int J Med*. 2017;110(9):565-570.
18. Rosenberg PB, Mielke MM, Appleby B, Oh E, Leoutsakos JM, Lyketsos CG. Neuropsychiatric symptoms in MCI subtypes: the importance of executive dysfunction. *Int J Geriatr Psychiatry*. 2011;26(4):364-372.
19. Geda YE, Roberts RO, Mielke MM, et al. Baseline neuropsychiatric symptoms and the risk of incident mild cognitive impairment: a population-based study. *Am J Psychiatry*. 2014;171(5):572-581.
20. Edwards ER, Spira AP, Barnes DE, Yaffe K. Neuropsychiatric symptoms in mild cognitive impairment: differences by subtype and progression to dementia. *Int J Geriatr Psychiatry*. 2009;24(7):716-722.
21. Pocnet C, Antonietti J-P, Donati A, Popp J, Rossier J, von Gunten A. Behavioral and psychological symptoms and cognitive decline in patients with amnestic MCI and mild AD: a two-year follow-up study. *Int Psychogeriatr*. 2015;27(8):1379-1389.
22. Pa J, Boxer A, Chao LL, et al. Clinical-neuroimaging characteristics of dysexecutive mild cognitive impairment. *Ann Neurol*. 2009;65(4):414-423.
23. Forrester SN, Gallo JJ, Smith GS, Leoutsakos J-MS. Patterns of neuropsychiatric symptoms in mild cognitive impairment and risk of dementia. *Am J Geriatr Psychiatry*. 2016;24(2):117-125.
24. Aalten P, de Vugt ME, Lousberg R, et al. Behavioral problems in dementia: a factor analysis of the neuropsychiatric inventory. *Dement Geriatr Cogn Disord*. 2003;15(2):99-105.
25. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the neuropsychiatric inventory. *J Neuropsychiatry Clin Neurosci*. 2000;12(2):233-239.
26. Schmidt M. *Rey Auditory Verbal Learning Test: A Handbook*. CA: Western Psychological Services Los Angeles; 1996.
27. Weintraub S, Salmon D, Mercaldo N, et al. The Alzheimer's disease centers' uniform data set (UDS): the neuropsychological test battery. *Alzheimer Dis Assoc Disord*. 2009;23(2):91-101.
28. Goodglass H, Kaplan E, Barresi B. *The Assessment of Aphasia and Related Disorders*. Philadelphia: Lippincott Williams & Wilkins; 2001.
29. AITB AITB. *Manual of directions and scoring*. Washington DC: Adjutant General's Office; 1944.
30. Petersen RC, Aisen P, Beckett L, et al. Alzheimer's disease neuroimaging initiative (ADNI) clinical characterization. *Neurol*. 2010;74(3):201-209.
31. Ivnik RJ, Malec JF, Smith GE, et al. Mayo's older Americans normative studies: WMS-R norms for ages 56 to 94. *Clin Neuropsychol*. 1992;6(S1):49-82.
32. Shirk SD, Mitchell MB, Shaughnessy LW, et al. A web-based normative calculator for the uniform data set (UDS) neuropsychological test battery. *Alzheimers Res Ther*. 2011;3(6):32.
33. Muthén L, Muthén B. *Mplus (Version 7.3) [computer software]*. (1998-2014). Los Angeles, CA: Muthén & Muthén:2014.
34. Rhemtulla M, Brosseau-Liard PÉ, Savalei V. When can categorical variables be treated as continuous? A comparison of robust continuous and categorical SEM estimation methods under suboptimal conditions. *Psychol Methods*. 2012;17(3):354-373.
35. Krull JL, MacKinnon DP. Multilevel modeling of individual and group level mediated effects. *Multivar Behav Res*. 2001;36(2):249-277.
36. Bondi MW, Smith GE. Mild cognitive impairment: a concept and diagnostic entity in need of input from neuropsychology. *J Int Neuropsychol Soc*. 2014;20(2):129-134.
37. Trzepacz PT, Yu P, Bhamidipati PK, et al. Frontolimbic atrophy is associated with agitation and aggression in mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement*. 2013;9(5):S95-S104. e101.
38. Linde RM, Dening T, Matthews FE, Brayne C. Grouping of behavioural and psychological symptoms of dementia. *Int J Geriatr Psychiatry*. 2014;29(6):562-568.
39. Connors MH, Seeher KM, Crawford J, Ames D, Woodward M, Brodaty H. The stability of neuropsychiatric subsyndromes in Alzheimer's disease. *Alzheimers Dement*. 2018;14(7):880-888.
40. van Dalen JW, Van Wanrooij LL, van Charante EPM, Richard E, van Gool WA. Apathy is associated with incident dementia in community-dwelling older people. *Neurol*. 2018;90(1):e82-e89.
41. Pink A, Stokin GB, Bartley MM, et al. Neuropsychiatric symptoms, APOE ε4, and the risk of incident dementia a population-based study. *Neurol*. 2015;84(9):935-943.
42. Peters ME, Schwartz S, Han D, et al. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache County dementia progression study. *Am J Psychiatry*. 2015;172(5):460-465.
43. Di Iulio F, Palmer K, Blundo C, et al. Occurrence of neuropsychiatric symptoms and psychiatric disorders in mild Alzheimer's disease and mild cognitive impairment subtypes. *Int Psychogeriatr*. 2010;22(4):629-640.
44. Balash Y, Mordechovich M, Shabtai H, Giladi N, Gurevich T, Korczyn A. Subjective memory complaints in elders: depression, anxiety, or cognitive decline? *Acta Neurol Scand*. 2013;127(5):344-350.
45. Glodzik-Sobanska L, Reisberg B, De Santi S, et al. Subjective memory complaints: presence, severity and future outcome in normal older subjects. *Dement Geriatr Cogn Disord*. 2007;24(3):177-184.
46. Bierman E, Comijs H, Jonker C, Beekman A. Effects of anxiety versus depression on cognition in later life. *Am J Geriatr Psychiatry*. 2005;13(8):686-693.
47. Beaudreau SA, O'hara R. The association of anxiety and depressive symptoms with cognitive performance in community-dwelling older adults. *Psychol Aging*. 2009;24(2):507-512.
48. Butters MA, Whyte EM, Nebes RD, et al. The nature and determinants of neuropsychological functioning in late-lifedepression. *Arch Gen Psychiatry*. 2004;61(6):587-595.
49. Hsiao JJ, Lu PH, Grill JD, Teng E. Longitudinal declines in instrumental activities of daily living in stable and progressive mild cognitive impairment. *Dement Geriatr Cogn Disord*. 2015;39(1–2):12-24.
50. Risacher SL, Shen L, West JD, et al. Longitudinal MRI atrophy biomarkers: relationship to conversion in the ADNI cohort. *Neurobiol Aging*. 2010;31(8):1401-1418.
51. Chow TW, Binns MA, Cummings JL, et al. Apathy symptom profile and behavioral associations in frontotemporal dementia vs dementia of Alzheimer type. *Arch Neurol*. 2009;66(7):888-893.
52. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment–beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. *J Intern Med*. 2004;256(3):240-246.
53. Donovan NJ, Amariglio RE, Zoller AS, et al. Subjective cognitive concerns and neuropsychiatric predictors of progression to the early clinical stages of Alzheimer disease. *Am J Geriatr Psychiatry*. 2014;22(12):1642-1651.
54. Ismail Z, Agüera-Ortiz L, Brodaty H, et al. The mild behavioral impairment checklist (MBI-C): a rating scale for neuropsychiatric symptoms in pre-dementia populations. *J Alzheimers Dis*. 2017;56(3):929-938.


**How to cite this article:** De Vito AN, Calamia M, Weitzner DS, Bernstein JPK; for the Alzheimer's Disease Neuroimaging Initiative. Examining differences in neuropsychiatric symptom factor trajectories in empirically derived mild cognitive impairment subtypes. *Int J Geriatr Psychiatry*. 2018;33:1627–1634. https://doi.org/10.1002/gps.4963