Journal of the International Neuropsychological Society (2025), 1–10
doi:10.1017/S1355617724000730

Research Article

Neuropsychiatric symptoms predict rate of change in executive function in Alzheimer's disease and related dementias

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Abstract

Objective: Neuropsychiatric symptoms (NPS) are considered diagnostic and prognostic indicators of dementia and are attributable to neurodegenerative processes. Little is known about the prognostic value of early NPS on executive functioning (EF) decline in Alzheimer's disease and related dementias (ADRD). We examined whether baseline NPS predicted the rate of executive function (EF) decline among older adults with ADRD. **Method:** Older adults ($n = 1625$) with cognitive impairment were selected from the National Alzheimer's Coordinating Center database. EF was estimated with a latent factor indicated by scores on Number Span Backward, Letter Fluency, and Trail Making-Part B. A curve of factors (CUFF) latent growth curve model was estimated to examine rate of change over four years. Baseline NPS severity was entered as a predictor in the model to examine its influence on the rate of change in EF over time. **Results:** The CUFF models exhibited good fit. EF significantly declined over four waves (slope = −.16, $p < .001$). Initial visit NPS severity predicted decline in EF (slope = .013, $p < .001$), such that those with greater baseline NPS severity demonstrated a more rapid decline in EF performance over time. Presence of 2 NPS significantly predicted EF decline, and those with medium total NPS severity (NPS score of 2–4) at baseline exhibited a sharper decline in EF. **Conclusions:** Findings underscore the importance of targeting NPS early across ADRD syndromes to minimize EF decline, offering novel insights into how early NPS treatment may alter cognitive trajectories. We provide an innovative, user-friendly web-based application that may be helpful for personalized treatment planning.

Keywords: Neuropsychiatric symptoms; executive function; longitudinal; Alzheimer's disease and related dementias; mild cognitive impairment; growth curve modeling

(Received 19 July 2024; final revision 5 December 2024; accepted 12 December 2024)

Introduction

Alzheimer's disease and related dementias (ADRD) are neurodegenerative disorders characterized by declines in memory, thinking skills, and day-to-day functioning. Alzheimer's disease (AD) is the most common cause of dementia, followed by vascular, Lewy body (DLB), and frontotemporal dementias (Goodman et al., 2017). Approximately 5 million people in the United States age 85 years and older have ADRD, and this prevalence is expected to more than double by 2025 (Office of the Assistant Secretary for Planning and Evaluation, n.d.). As of 2019, the global economic burden of ADRD was $2.8 trillion, and this is expected to increase to $16.9 trillion by 2050 (Nandi et al., 2022). This looming societal health and economic burden provides the impetus for research on sensitive, patient-specific methods of early disease identification and monitoring.

There has been increased attention on executive functioning (EF) decline and neuropsychiatric symptoms (NPS) in ADRD, given their importance for differential diagnosis (Guarino et al., 2019; Pakzad et al., 2018), and functional decline (Cahn-Weiner et al., 2003; Farias et al., 2003; Gallo et al., 2008; Razani et al., 2007), and conversion from MCI to dementia (Acosta et al., 2018; David et al., 2016; Edwards et al., 2009; Jung et al., 2020; Teng et al., 2007). EF represents "higher-order" cognitive processes (e.g., inhibitory control, working memory, initiation, cognitive flexibility, problem solving, decision-making, emotion regulation) (Diamond, 2013; Suchy, 2015) that subserve complex, goal-directed tasks and behaviors (e.g., preparing food, managing medications and finances, etc.) (Gauthier & Gauthier, 1990; Lezak, 2012). NPS (e.g., apathy, depression, aggression/agitation, anxiety, and irritability) (Devanand et al., 2022; Zhao et al., 2016) are common among ADRD syndromes, and presence and severity of NPS predict decreased quality of life (Kwon & Lee, 2021; Lyketsos et al., 2000; Martin & Velayudhan, 2020; Sadak et al., 2014). Executive dysfunction (Allain et al., 2013; Carlson et al., 2009; Duarte-Abritta et al., 2021; Guarino et al., 2019; Harrington et al., 2013) and NPS (Apostolova & Cummings, 2008; Diniz et al., 2013; Gallagher et al., 2017; Kwon & Lee, 2021; Leoutsakos et al., 2015) are evident in pre-clinical ADRD and throughout disease progression, and can be considered relevant cross-diagnostic features across ADRD syndromes (Johns et al., 2009; Kwon & Lee, 2021; Ramirez-Gomez et al., 2017).

Shared neurobiological and clinical mechanisms may provide opportunities for development of generalizable, transdiagnostic

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Cite this article: Goodwin G.J., Briley D.A., Singsank K., Tanner D., Maloy-Robertson M., & John S.E. Neuropsychiatric symptoms predict rate of change in executive function in Alzheimer's disease and related dementias. *Journal of the International Neuropsychological Society*, 1–10, https://doi.org/10.1017/S1355617724000730

interventions in ADRD (Zeng et al., 2023). EF and NPS are both considered frontally mediated processes, implying overlapping pathology in ADRD (Bruen et al., 2008; J. Cummings, 2020; J. L. Cummings, 1993; J. Cummings & Mega, 2003; Godefroy, 2003). Cross-sectional research examining the association between NPS and EF in ADRD further highlights overlapping clinical mechanisms (Chen et al., 1992; García-Alberca et al., 2011). For example, agitation and disinhibition were associated with deficits in planning, organization, inhibitory control, and selective and divided attention (De Lucia et al., 2023). However, there is limited research on the predictive role of NPS on the longitudinal trajectory of EF, which hinders our understanding of how these factors interact over time.

Recent longitudinal studies have shown mixed findings on the predictive role of NPS on EF over time. Two studies have shown that NPS predict more rapid cognitive decline over time in cognitively normal older adults (Burhanullah et al., 2020; Krell-Roesch et al., 2021). One study found that higher baseline NPS severity predicted steeper decline on EF tasks over time in patients with MCI due to probable Lewy body disease and Parkinson's disease (Wright et al., 2023). In contrast, baseline NPS had no effect on cognitive functioning over time in patients with subjective cognitive decline, MCI, or probable AD (Eikelboom et al., 2021).

Mixed findings may be the result of the measurement and modeling approaches used in these studies. First, EF was operationalized using only one test (Burhanullah et al., 2020) or with a composite score derived from a global cognitive screening measure (e.g., the Mini-Mental State Examination) (Eikelboom et al., 2021; Wright et al., 2023); neither approach captures the full range and extent of EF abilities. Further, manifest variables—those that are directly observed—do not account for measurement error (e.g., variability in task administration) or the interaction among measures (e.g., association between two EF tasks). Second, linear mixed effects modeling does not offer as much flexibility or nuance compared to other approaches, as it assumes both linear change over time and a linear relationship between domains of interest. In other words, this approach assumes that 1) EF is a static construct that declines at a steady rate, and 2) the relationship between NPS and EF is consistent over time. Thus, important information about dynamic, nonlinear associations between NPS and EF decline might be missed (McNeish & Matta, 2018).

Latent growth curve modeling (LGCM) is considered the gold standard approach for modeling growth and decline over time in developmental psychology (Nesselroade, 1991) and cognitive aging research (McArdle et al., 2004, 2009; Ng et al., 2023) because it provides precise estimates of intra- and inter-individual change. This model suggests that a single trajectory underlies growth or decline over time, allowing for strong and reliable estimates of 1) how things change over time and 2) what factors are associated with those changes (Ferrer et al., 2008; Liu & Chang, 2010; McArdle, 2009). LGCM also allows for flexible estimation of nonlinear change (e.g., differences in rate of change in EF over time) (Grimm et al., 2011; McNeish & Matta, 2018). For example, one study used LGCM to examine the relationship among cognitive domains over time among cognitively normal older adults. Findings showed subtle declines in EF/attention and processing speed, while language and memory scores improved over time. Additionally, lower EF at baseline predicted decline in memory over time, suggesting that intact baseline EF is important for preserving memory functioning throughout aging (MacAulay et al., 2018). A separate study used LGCM to model longitudinal change in neuropsychological performance in MCI and found that EF declined more rapidly than all other neurocognitive domains, suggesting intra-individual variability in cognitive decline (Johnson et al., 2012). Therefore, LGCM may offer a more robust approach to estimating within- and between-person differences in the association between baseline NPS and longitudinal EF.

The present study

Precise research is needed to clarify the trajectory of EF decline in ADRD as well as the predictive role of early NPS on EF decline. Evaluation of NPS effects on EF decline over time among patients with ADRD may provide novel insights into the prognostic value of NPS and elucidate shared frontally mediated symptom presentations. Such insights are essential for advancing prognostic accuracy and identifying critical time points for targeted intervention. This study used the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) to examine whether baseline NPS severity predicts rate of decline in EF in older adults with ADRD over four years. We modeled inter- and intra-individual patterns of EF change over time using second-order latent growth curve modeling. We expected that those with higher baseline NPS severity would exhibit more accelerated decline in EF.

Method

The NACC UDS provides a comprehensive data repository for research on neurodegenerative disorders. While the primary disorder of interest is Alzheimer's disease, several other neurodegenerative conditions are included in the database and patients with ADRD are followed over time. The UDS contains longitudinal data that have been collected since 2005 at NIA-funded Alzheimer's Disease Research Centers (ADRCs) across the United States. Data elements and collection methods have been described previously (Beekly et al., 2004, 2007; Besser et al., 2018; Morris et al., 2006). The NACC UDS includes neuropsychological, behavioral, medical, and health history data in order to accurately diagnose neurodegenerative disease and track its course (Morris et al., 2006). Participants and study partners enrolled at each ADRC provide written consent as part of the IRB-approved protocol at that site. This consent covers both the data collection procedures required by the respective center as well as the inclusion of the participant's data in the larger NACC UDS database.

Participants

Participants were selected from the NACC UDS (v3-v3.2) data set (https://naccdata.org/). Patient evaluations were completed at funded ADRCs during the period between March 2015 and the freeze date of June 2023. Patient demographic variables and diagnostic status were used to identify the sample for analysis (Supplementary Figure 1). Data were included from four study visits: baseline (wave 0), 1 year (wave 1), 2 years (wave 2), and 3 years (wave 3). The following inclusionary criteria were applied for sample identification: participants aged 50 years or older; participants completed a baseline evaluation during UDS v3 or v3.2; and participants completed evaluations across the four consecutive waves ($n = 3{,}770$ after initial selection criteria). Participants were excluded if their cognitive status was "normal cognition" at all waves (excluded $n = 1{,}844$), if they were diagnosed as cognitively impaired due to a non-neurodegenerative etiology (i.e., "cognitively impaired, not MCI"; excluded $n = 293$), and if

https://doi.org/10.1017/S1355617724000730 Published online by Cambridge University Press

their cognitive data were considered invalid according to clinician report (excluded $n = 8$).

Measures

Race and ethnicity

In order to examine participant race and ethnicity, a new variable was calculated that combined data from the NACC-derived race variable for the six main census race groups and the UDS ethnicity variable for Hispanic/Latino ethnicity. Five new racial/ethnic groups were created from these data: non-Hispanic white, Hispanic white, non-Hispanic Black, Hispanic Black, and all other categories.

Cognitive status and dementia etiology

Cognitive status and etiologic diagnosis for each patient was determined through a formal process at each ADRC using the 2011 National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines (Albert et al., 2011; Besser et al., 2018). Diagnoses are assigned by either a consensus panel of experts or by the single physician conducting the examination, and this varies by center. Cognitive impairment includes the following categories: 1) normal cognition, 2) impaired-not-MCI (subjects who are cognitively impaired due to non-neurodegenerative etiology), 3) MCI (subjects with either amnestic or non-amnestic MCI), and 4) dementia (subjects who have a diagnosis of dementia) (Petersen & Morris, 2005). We excluded from our analytic sample all those with an "impaired-not-MCI" diagnosis. Participants were also excluded if their diagnostic severity was rated "normal cognition" across all four waves. Etiology of impairment includes the following categories, which are available for each of the neurodegenerative disorders (AD, DLB, Vascular, frontotemporal lobar degeneration [FTLD]): 1) primary (e.g., AD is the primary cause of observed cognitive impairment) and 2) contributing (e.g., AD is a contributing cause of observed cognitive impairment (Morris et al., 2006). See Supplementary Figure 1 for a detailed description of sample selection.

Characterization variables

The Geriatric Depression Scale (GDS) is a self-report measure of depression symptoms (Yesavage & Sheikh, 1986). Patients rate whether they experienced 15 depression symptoms over the last week (0 = *No*, 1 = *Yes*). Scores are summed with scores of 9–11 indicating moderate depression and scores of 12–15 indicating severe depression. The Clinical Dementia Rating (CDR®) Dementia Staging Instrument is a 5-point scale that characterizes six domains of cognitive and functional abilities (Morris, 1993). Information is obtained through semi-structured interview of the patient and informant, and clinicians rate the patient's level of overall impairment (0.0 = *No impairment*–3.0 = *Severe Impairment*).

Model variables

Neuropsychiatric symptoms

The NPI-Q is a widely used measure to assess neuropsychiatric symptoms among clinical populations (Kaufer et al., 2000). The NPI-Q relies on a caregiver/informant report of the presence and severity of 12 neuropsychiatric symptoms evident within the past month. Assessed symptoms include delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, nighttime behaviors, and appetite/eating problems (Kaufer et al., 2000). Informants endorsed the presence (0 = *No*, 1 = *Yes*) and severity (1 = *Mild*, 2 = *Moderate*, 3 = *Severe*) of each symptom. The total NPI-Q symptom severity score is calculated by summing the severity score for each symptom (range 0–36). The NPI-Q has adequate psychometric properties, including acceptable test–retest reliability and convergent validity (Kaufer et al., 2000).

Executive functioning

Three measures in the NACC UDS v.3 neuropsychological battery provide distinct values of EF (e.g., phonemic fluency, working memory, set-shifting/cognitive flexibility) and were used to estimate a single EF factor. Phonemic Fluency (2-letter version) is a measure of speeded word generation in response to phonemic cues. Participants are asked to name items that begin with a certain letter, and the number of unique correct responses are scored. Possible scores range from 0 to 80 points (Besser et al., 2018). Number Span Backward is a measure of working memory. Numbers are presented orally and participants are asked to recall the numbers in reverse order; item difficulty increases in ascending order. We use the number of correct trials as a total score in the model, which ranges from 0 to 14 (Besser et al., 2018). Trail Making Test Part B (TMT-B) is a measure of set-shifting and cognitive flexibility. Participants are asked to draw lines in number and letter order while shifting between numbers and letters. Total time to complete the task is scored with possible scores ranging from 0 to 300 s (Reitan & Wolfson, 1993).

Analyses

Statistical analyses were conducted in *R* version 4.0.3 using the *lavaan* package (Roseel, 2012). NPI-Q severity scores and TMT-B scores were reverse scored so that higher scores indicated better functioning across all measures. Analyses were conducted in three stages. First, confirmatory factor analysis (CFA) was used to model EF from the three EF measures, and measurement invariance was examined across waves. Second, a curve-of-factors (CUFF) latent growth curve model was then used to examine rate of change in the EF factor across waves. Third, structural regression was used to examine whether NPS severity at W0 predicted rate of change in the EF factor over four waves (Ferrer et al., 2008).

Measurement invariance of executive functioning

CFA was used to estimate the executive function factor from Number Span Backward, Letter Fluency, and TMT-B (Staffaroni et al., 2021). Full information maximum-likelihood (FIML) estimation and maximum likelihood with robust standard errors (MLR) estimation were used as they are robust to missingness and non-normality, respectively (Enders & Bandalos, 2001). Four nested models were compared to test measurement invariance across the four waves: configural invariance model (establishes model specification equivalence), metric invariance model (establishes equivalence of factor loadings), scalar invariance model (establishes equivalence of intercepts), and strict invariance model (establishes equivalence of residuals). Models are considered invariant if there is no significant reduction in model fit at any step. The configural model had the following identification constraints: all factor loadings and intercepts were freely estimated; the mean and variance of all factors were set to 0 and 1, respectively, (creating a standardized latent factor). Correlations

https://doi.org/10.1017/S1355617724000730 Published online by Cambridge University Press

were permitted between factors at each time point, and temporal correlations were permitted between like indicators at each wave. In the nested metric model, factor loadings were set to be equivalent across time, and constraints on the factor variances were removed for wave 1 through wave 3. In the nested scalar model, indicator intercepts were set to be equivalent across time, and constraints on the factor means were removed for wave 1 through wave 3. In the nested strict model, indicator residual variances were set to be equivalent across time.

Overall model fit was determined using χ^2 goodness-of-fit test, comparative fit index (CFI), and root mean square error of approximation (RMSEA). A nonsignificant p value suggests adequate model fit for the χ^2 test; however, this test is affected by large sample sizes (Cheung & Rensvold, 2002; Hu & Bentler, 1999). Fit indices were considered satisfactory when CFI > .95 and RMSEA < .06 (Hu & Bentler, 1999). Model comparisons were analyzed using change in chi-square ($\Delta\chi^2$) and change in CFI (ΔCFI) (Cheung & Rensvold, 2002).

Longitudinal change in EF predicted by NPS

Longitudinal change in EF was assessed using a second-order growth model, or curve-of-factors (CUFF) LGCM (Ferrer et al., 2008; Tisak & Meredith, 1990), in which change is modeled at the latent level over time. The CUFF model is an extension of the LGCM; while the LGCM estimates change of observed variables (e.g., raw scores or composite scores) over time, the CUFF model measures change at the latent level over time. Differently stated, the CUFF model fits a growth curve to factor scores (hence "curve-of-factors") and estimates longitudinal change of the latent factors (Ferrer et al., 2008). First, the strict temporal invariance CFA model was estimated, which consisted of four factors: Wave 0 EF, Wave 1 EF, Wave 2 EF, and Wave 3 EF, with added constraints for identification purposes. Letter Fluency and TMT-B were rescaled (Letter Fluency/10; TMT-B/1000) to help with residual variance estimation. We then fit a growth curve to these four factors. Growth parameters were estimated to examine the intercept and slope (i.e., rate of change in EF), and the association between intercept and slope at the latent level. The intercept factor loadings were constrained to be constant across waves with loadings of 1 for all time points. The slope factor loadings had fixed coefficients of 0, 1, 2, and 3 to reflect each visit. Latent EF factor means were constrained to be 0 to model change in EF with the intercept and slope factors. The intercept factor mean and variance were constrained to be 0 and 1, respectively, for identification purposes. This specification is consistent with fixing the latent EF mean and variance at baseline to 0 and 1 to establish a standardized latent factor at baseline. The slope factor mean and variance were freely estimated. The intercept and slope latent factors were regressed on baseline NPI-Q total symptom severity scores to estimate the predictive value of baseline NPS total severity on EF decline.

Results

The final sample ($n = 1{,}625$) consisted of older adults ($M_{W0\text{age}} = 71.3$, $SD_{W0\text{age}} = 8.18$; 46.7% female, $M_{\text{education}} = 16$ years, $SD_{\text{education}} = 2.91$ years) who predominantly identified as non-Hispanic white (79.4% non-Hispanic white, 9.5% non-Hispanic Black, 5.6% Hispanic white, 5.1% other, 4% Hispanic Black). The majority of the sample met criteria for MCI at W0 (48%), and a large percentage of the sample met criteria for dementia at waves 1–3 (W1: 44.9%; W2: 50.7%; W3: 55.8%). AD was the presumed primary etiology for cognitive impairment for the majority of the sample across all waves followed by FTLD, Lewy body disease, and cerebrovascular disease (Table 1). On average, 1 or more symptoms were endorsed on the NPI-Q at W0 (median number of symptoms = 2, min = 0, max = 11). Among those who endorsed symptoms at W0, total NPS severity was low overall (median total symptom severity = 3, min = 1, max = 26). The most frequently endorsed symptom at W0 was anxiety (31.44%), followed by irritability/lability (31.35%), and depression/dysphoria (30.32%). Hallucinations were the least frequently endorsed symptom at W0 (3.94%). See Table 2 for additional characterization of NPS severity at W0.

Table 1. Participant demographics stratified by time point

Sample Characteristics by Wave ($n = 1{,}625$ people)	Wave 0	Wave 1	Wave 2	Wave 3
Age [M(*SD*)]	71.3 (8.18)	72.5 (8.18)	73.6 (8.18)	74.8 (8.20)
Sex (N)				
Male	866	—	—	—
Female	759	—	—	—
Education Years [M(*SD*)]	16 (2.91)	—	—	—
Ethnic Racial Group (%)				
non-Hispanic white	79.4%	—	—	—
non-Hispanic Black	9.5%	—	—	—
Hispanic white	5.6%	—	—	—
Hispanic Black	4.0%	—	—	—
Other	5.1%	—	—	—
Cognitive Status at Visit (%)				
Normal Cognition	233 (14.3%)	220 (13.5%)	209 (12.9%)	181 (11.1%)
MCI	780 (48%)	676 (41.6%)	592 (36.4%)	537 (33.0%)
Dementia	612 (37.7%)	729 (44.9%)	824 (50.7%)	907 (55.8%)
Alzheimer's Disease Etiology (N)				
Primary	965	974	961	969
Contributing	36	30	39	55
Lewy Body Disease Etiology (N)				
Primary	94	100	110	113
Contributing	15	21	25	30
FTLD Disease Etiology (N)				
Primary	104	105	105	103
Contributing	11	12	8	9
Vascular Disease Etiology (N)				
Primary	56	58	58	65
Contributing	70	75	90	96

Note: Etiology variables may not add up to 1,625 as 1) there may be overlapping etiologies, 2) etiology diagnosis might change over time, and 3) there are other classifications that are not included here. All totals are relative to a given etiology category. *M* = mean, SD = standard deviation, MCI = mild cognitive impairment, FTLD = frontotemporal lobar degeneration. Disease etiology derived from clinician diagnosis of cause of observed cognitive impairment due to Alzheimer's disease, Lewy Body Disease, FTLD, or vascular diseases. Other* ethnoracial group includes those identifying as Asian, American Indian/Alaska Native, Native Hawaiian or Other Pacific Islander, Multiracial, and Unknown.

Cognitive variables met assumptions for normal distribution (skewness < |1.0|; 2 > kurtosis < 4) for all variables across all time points, and NPI-Q at W0 did not meet assumptions for normality (skewness = 2.02; kurtosis = 7.93) (Field, 2013) (Table 3). Thus, FIML with MLR was used in all models, and robust fit statistics are reported. Results from the three structural equation models are discussed separately, below.

Measurement invariance over time

Table 4 provides the model fit for the measurement invariance models. Strict measurement invariance was established at all

https://doi.org/10.1017/S1355617724000730 Published online by Cambridge University Press

Table 2. Frequency of neuropsychiatric symptom severity ratings at wave 0 by symptom and overall total

Wave 0 Frequencies of Neuropsychiatric Symptom Severity Levels				
Symptom	Symptoms Not Present	Mild	Moderate	Severe
Delusions	94.51%	3.10%	1.87%	0.52%
Hallucinations	96.06%	3.10%	0.58%	0.26%
Agitation/Aggression	79.99%	12.07%	6.97%	0.97%
Depression/Dysphoria	69.73%	21.93%	7.18%	1.16%
Anxiety	68.61%	20.45%	9.58%	1.36%
Elation/Euphoria	95.41%	3.30%	1.10%	0.19%
Apathy/Indifference	75.02%	15.86%	6.67%	2.46%
Disinhibition	85.70%	9.13%	4.01%	1.17%
Irritability/Lability	68.74%	20.71%	8.74%	1.81%
Motor Disturbance	89.39%	6.08%	3.30%	1.23%
Nighttime Behaviors	78.60%	11.95%	7.88%	1.58%
Appetite/Eating Problems	82.32%	11.33%	5.12%	1.23%
	Absent Symptoms (0)	Low Total Severity (1)	Medium Total Severity (2-4)	High Total Severity (>4)
Total Symptom Severity	33.80%	15.00%	27.70%	23.50%

Note: Neuropsychiatric symptom ratings derived from the NPI-Q. Item-level ratings: symptom not present = 0, mild = 1, moderate = 2, severe = 3. Total Symptom Severity score takes the sum of each of the 12 symptom severity scores. Total Symptom Severity Score range = 0-26. Based on quantiles, the following item-level ratings were applied to the Total Symptom Severity score: no symptoms reported on any items ("absent symptoms") = 0, "low severity" overall = 1, "medium severity" overall = 2-4, and "high severity" overall > 4.

Table 3. Cognitive & neuropsychiatric characteristics stratified by time point for overall sample

Descriptive Statistics by Wave (n = 1,625)				
	Wave 0	**Wave 1**	**Wave 2**	**Wave 3**
CDR Global Impairment Rating (%)				
None (0.0)	270 (16.6%)	227 (14%)	213 (13.1%)	204 (12.6%)
Questionable (0.5)	1054 (64.9%)	941 (57.9%)	801 (49.3%)	688 (42.3%)
Mild (1.0)	248 (15.3%)	328 (20.2%)	387 (23.8%)	344 (21.2%)
Moderate (2.0)	43 (2.6%)	94 (5.8%)	163 (10.0%)	234 (14.4%)
Severe (3.0)	10 (.6%)	35 (2.2%)	61 (3.8%)	155 (9.5%)
Depression Total Score[M(*SD*)]	2.18 (2.31)	2.11 (2.20)	2.15 (2.21)	2.30 (2.35)
NPS Severity [M(SD)]	2.91 (3.80)	3.24 (4.00)	3.82 (4.53)	4.26 (4.83)
Min-Max	0–26	0–28	0–26	0–30
Skewness	2.02	1.93	1.78	1.63
Kurtosis	7.93	7.92	6.67	6.15
Trail Making Test Part B [M(SD)]	133 (76.9)	137 (78.4)	143 (81.2)	147 (85.2)
Min-Max	17–300	24–300	29–300	37–300
Skewness	1.13	1.02	0.87	0.81
Kurtosis	3.1	2.83	2.45	2.25
Numbers Backward [M(SD)]	5.52 (2.25)	5.48 (2.31)	5.44 (2.25)	5.48 (2.39)
Min-Max	0–13	0–14	0–14	0–14
Skewness	0.16	0.18	0.06	0.19
Kurtosis	3.01	3.16	3.13	3.07
Letter Fluency [M(SD)]	22.9 (9.13)	22.8 (9.20)	22.6 (9.05)	22.5 (9.21)
Min-Max	0–55	0–55	0–56	0–58
Skewness	0.17	0.07	0.11	0.1
Kurtosis	2.79	2.79	2.97	2.83

Note: M = mean, SD = standard deviation, Min = minimum, Max = maximum, CDR = clinical dementia rating, NPS = neuropsychiatric symptoms. CDR impairment ratings derived from the Clinical Dementia Rating Global Impairment score. Depression derived from Geriatric Depression Scale total score. NPS derived from Neuropsychiatric Symptom Inventory Questionnaire (NPIQ) total severity score. Descriptive statistics are based on raw variables.

four stages, suggesting that the EF factor is time-invariant (see Supplementary Figure 2). The largest ΔCFI was .008, which suggests imposing measurement invariance constraints do not substantially worsen model fit.

Decline in EF over time

We initially attempted to freely estimate the latent EF factor variances, but we encountered a Heywood case (i.e., negative variance estimate). We fit alternative specifications that fixed variances to 0, equated variance estimates across waves (i.e., equivalent residual EF variance at each wave), or constrained the variances for the Heywood case (i.e., EF W0) to be positive (Supplementary Table 1). All models are included in the supplemental materials, and all models imply the same substantive conclusions. We focus here on the best fitting model without a Heywood case, a model in which we fixed EF factor variance estimates at W0 to be greater than 0.

Using the strict invariance model, a CUFF model was estimated to examine rate of change in EF over time (see Supplementary Figure 3). The CUFF model exhibited good fit ($\chi^2[57] = 195.44$, $p < .001$; CFI = .98, RMSEA = .04). EF declined at a rate of .16 SDs per wave ($p < .001$). Differently stated, participants with average EF at baseline (standardized M_{EF} at W0 = 0) would be expected to decline .48 SDs by W3 (Table 5). EF intercept and slope were positively correlated ($r = .25$), such that the higher initial EF scores

https://doi.org/10.1017/S1355617724000730 Published online by Cambridge University Press

Table 4. Measurement invariance analysis results

Model	χ^2 (*df*)	$\Delta\chi^2$	CFI	ΔCFI	RMSEA
Configural	76.31(30)*		0.99		0.03
Metric	84.85(36)**	8.54	0.99	0[a]	0.029
Scalar	152.51(42)**	67.7**	0.986	−0.008[a]	0.04
Strict	189.53(51)**	37.0**	0.982	−0.004[a]	0.04

Note: Robust fit statistics are reported. $\Delta\chi^2$ = change in χ^2. CFI = comparative fit index. ΔCFI = change in CFI. RMSEA = root mean-square error of approximation. *$p < .05$. **$p < .001$. [a]This step was determined to be invariant.

Table 5. Model implied decline in EF based on baseline NPS severity

	Decline in EF (SDs)		
Baseline NPS Severity	**W0 to W1**	**W1 to W2**	**W2 to W3**
Absent NPS	−0.16	−0.32	−0.48
Median NPS Severity (NPS = 2)	−0.19	−0.37	−0.56
Severe NPS (NPS = 10)	−0.29	−0.58	−0.87
Highest NPS Severity (NPS = 26)	−0.50	−1.00	−1.49

Note: Values represent decline in EF from wave to wave based on baseline NPS severity. Values are in standard deviation (SD) units. Model-implied intercept (slope when NPS = 0) = −.16. Model-implied slope (when NPS >0) = .013.

were, the less decline in EF over time. The slope variance estimate (slope variance = .05, $p < .001$) suggests that people slightly differ in their rate of EF decline (i.e., some people decline at a faster rate than others).

NPS Predicting EF Decline over time

Baseline NPI-Q total symptom severity score was entered as a predictor in the CUFF model to determine the predictive value of baseline NPS on EF rate of decline. The model exhibited good fit ($\chi^2[67] = 198.93$, $p < .001$; CFI = .98, RMSEA = .04). NPS total symptom severity at W0 predicted decline in EF ($p < .001$), such that those with greater total NPS severity at W0 decreased more rapidly in EF over time (Figure 1). For every point increase in total NPS severity, participants declined in EF by an additional .013 SD (small effect) per year (Supplementary Figure 4). For example, for participants with W0 NPS severity at the median (total NPS severity = 2), they would decline an additional −.56 SDs in EF by W3. For participants with the highest level of symptom severity at W0 (total NPS severity = 26), they would decline an additional −1.49 SDs in EF by W3 (Table 5). Like the EF CUFF model, the slope variance estimate (slope variance = .05, $p < .001$) suggests that people slightly differ in their rate of EF decline (i.e., some people decline at a faster rate than others). Model-implied indices were used to develop an open access, interactive, web-based application [available at: https://gracejgoodwin.shinyapps.io/GrowthCurveEFapp/] allowing users to observe EF trajectories as a function of baseline NPS severity (Supplementary Figure 5).

Post hoc robustness check

We performed two checks to determine the robustness of our findings. First, we tested whether extreme NPI-Q outliers were driving effects in the CUFF model. We Winsorized NPI-Q total symptom severity scores that were greater than three standard deviations from the mean to the next highest value (Wilcox, 1993). We used the Winsorized NPI-Q total symptom severity score in the predicted CUFF model to determine whether effects were consistent without extreme cases. There was a statistically significant effect of total NPS severity on rate of decline suggesting that outliers were not exclusively driving effects.

Second, we tested whether the association between total NPS severity and EF decline was linear. We created quantiles for the W0 NPI-Q severity variable (median = 2), which equally split the data into 4 categories: "absent symptoms" (NPI-Q total symptom severity = 0), "low severity" (NPI-Q total symptom severity = 1), "medium severity" (NPI-Q total symptom severity = 2–4), "high severity" (NPI-Q total symptom severity > 4). The absent symptom and low severity groups were roughly equivalent to one another, implying that NPS does not have a sizeable impact on EF levels or trajectories at lower levels. However, for participants scoring above the median, NPS was associated with lower EF levels (in an approximately linear manner) and quicker rate of EF decline. The rate of EF decline was similar for the medium and high groups, implying that above a medium baseline NPS severity threshold, EF deficits magnify over time. Given that the NPI-Q total score is used clinically, we chose to retain the continuous variable in our final CUFF model. However, future work with larger samples would be required to more precisely identify the baseline severity threshold for detrimental EF prognosis (Supplementary Table 2).

Discussion

The present study examined whether initial visit NPS severity predicted rate of EF decline over time in ADRD. We used second-order LGCM to identify inter- and intra-individual differences in the association between NPS at initial visit and rate of change in EF. Consistent with expectations, those with greater total NPS severity at baseline exhibited a more rapid rate of EF decline over four years.

Prevalence of neuropsychiatric symptoms at initial visit

The majority of our sample met criteria for MCI at W0 and there was a higher prevalence of dementia at each subsequent wave. Much of our sample remained in the same diagnostic category across sequential visits, though we observed disease conversion, as seen through the shifting sample proportions between MCI and dementia over 4 years. NPS burden at W0 was generally low, which is representative of early clinical presentations of MCI (Edwards et al., 2009; Lyketsos et al., 2002). A median of 2 NPS items were endorsed at W0, and of those who reported symptoms, the majority endorsed mild symptom severity. Consistent with previous research, the most frequently endorsed NPS were irritability/lability, anxiety, and depression/dysphoria, while psychotic symptoms were less common (Lyketsos et al., 2002; Martin & Velayudhan, 2020). Though symptom burden was generally low at W0 for the overall sample, presence of at least one symptom and low NPS severity at early stages has been shown to increase risk for conversion to dementia (Peters et al., 2013). In particular, irritability and depression predict conversion from MCI to dementia (AD and non-AD dementias) independent of age, education, cognitive screener score, and apolipoprotein E status (Mourao et al., 2016; Roberto et al., 2021).

Change in EF over time

Latent growth curve analysis showed that participants significantly declined in EF over time within a sample of participants with

https://doi.org/10.1017/S1355617724000730 Published online by Cambridge University Press

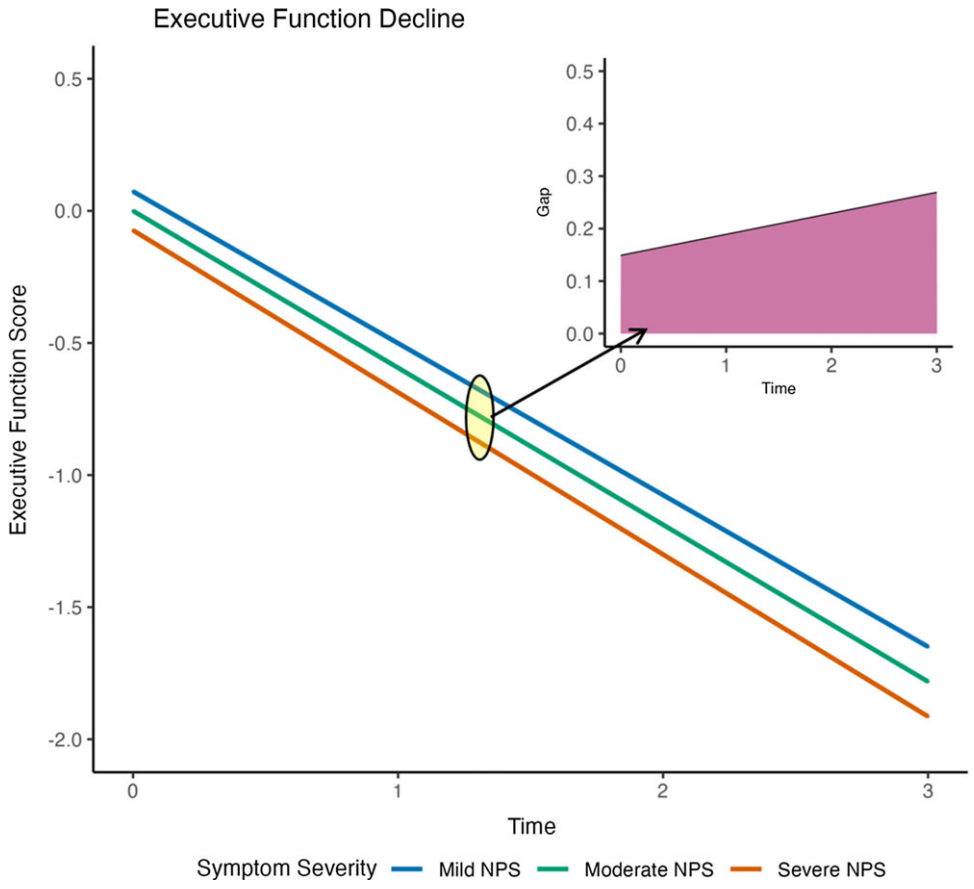

Figure 1. Model-implied trajectory of executive function decline by NPS severity. *Note*: Main Graph: depicts model-implied differences in EF decline by NPS severity group. EF = executive functioning. NPS = neuropsychiatric symptoms. *X*-axis represents time points that correspond to annual visits (0 = wave 0, 1 = wave 1, 2 = wave 2, 3 = wave 3). *Y*-axis represents model-implied EF score. Mild NPS group refers to people with NPS at −1.5 standard deviations below the raw NPS mean. Moderate NPS refers to people with NPS at the NPS mean. Severe NPS refers to people with NPS scores at 1.5 standard deviations above the NPS mean. These labels do not correspond to item ratings with similar labels. Inset Graph: depicts the magnitude of the difference in EF decline between groups over time. *X*-axis represents time points; *Y*-axis represents expected gap between mild and severe NPS on EF. W0 gap between EF performance between mild NPS and severe NPS = .148 intercept-SDs; W1 gap = .188; W2 gap = .228; W3 gap = .268. The gap in EF performance nearly doubles between mild and severe NPS by W3.

mixed ADRD etiologies. There were inter-individual differences in the rate of EF change, such that higher EF scores at initial visit were associated with less EF decline over time. There was also intra-individual variability in the rate of change, such that the level of EF decline varied from wave to wave. In contrast, raw score means of EF measures remained stable (Number Span Backward, Letter Fluency) or slightly declined (TMT-B) over the four waves, obscuring more nuanced trends in susceptibility and rate of decline and showcasing the added information gained from a latent growth curve approach. Findings are consistent with studies using latent growth curves to model change in EF over time in MCI: EF declines over time in AD and there is significant variability in rate of decline in EF over time (Gustavson et al., 2021; Johnson et al., 2012). While we did not compare EF with other cognitive domains, previous literature suggests that EF may decline earlier than memory, highlighting the importance of tracking non-memory cognitive domains for early detection and timely intervention. Some studies have shown inconsistent patterns of EF change over time in ADRD, likely due to measurement error and variable sensitivity across EF scales (Eikelboom et al., 2021; Guarino et al., 2019). Our robust approach allows for examination of nuanced inter- and intra-individual variability in rate of decline in EF over time.

NPS as a prognostic marker for executive function decline

As expected, NPS severity at initial visit predicted rate of change in EF, such that those who had greater NPS severity at their initial visit had more rapid decline in EF over time. While the influence of NPS on the slope of EF decline is small, the longitudinal effect on EF is notable and clinically meaningful. While NPS burden was generally low at W0, those with only two symptoms at initial visit still showed more rapid decline in EF over four years relative to those without symptoms. Moreover, compared to absent symptoms and low symptom severity, those with medium levels of NPS severity at initial visit (NPS = 2–4) demonstrated a sharper decline in EF. This pattern was evident within a sample of mixed neurodegenerative etiologies, supporting the generalizability of findings. Similar to our results, other investigations of NPS severity have revealed those with moderate NPS burden at early stages may be at greater risk for executive dysfunction and associated functional decline (Gallo et al., 2008; Razani et al., 2007). Our findings are also consistent with previous work that showed baseline NPS were associated with more rapid decline in non-executive cognitive tasks, including word list memory, animal fluency, and praxis recall (Burhanullah et al., 2020). Specific NPS have also been shown to predict accelerated decline across cognitive domains (Zainal & Newman, 2023). For example, among community dwelling cognitively normal older adults or adults with MCI, mild NPS have also been shown to predict more accelerated decline across several cognitive domains (e.g., memory, attention, language, and visuospatial skills). This work also identified specific NPS (i.e., apathy, depression, nighttime behaviors) that were responsible for greater decline across domains, pointing to their use as prognostic markers (Krell–Roesch et al., 2021). While examining the association between specific NPS and rate of EF

https://doi.org/10.1017/S1355617724000730 Published online by Cambridge University Press

decline was beyond the scope of the present work, it is an important future direction that will pinpoint specific symptoms that may be responsible for this pattern.

Limitations and future directions

There are several limitations to the present study. While we included a diverse sample representing several ADRD syndromes, the majority of participants were diagnosed with AD. While our sample is consistent with disease base-rates (i.e., AD is more common than other related dementias) (Goodman et al., 2017), future research sampling a more balanced and representative group of ADRD syndromes will identify disease-specific associations between NPS and EF. Additionally, as is true of the overall trends with the NACC sample, our analysis consisted of predominantly highly educated, non-Hispanic white participants, which limits the generalizability of our findings to diverse groups. Future research with minoritized samples is essential to identify differences in the association between EF and NPS and to improve access to individualized care. Relatedly, the NPI-Q symptom descriptions may be susceptible to cultural bias or strongly associated with other comorbid conditions among different ethnoracial groups. These interpretative differences can influence symptom endorsement patterns (Babulal et al., 2023). Additionally, the NPI-Q does not include information about frequency of experienced symptoms (e.g., once per week, several times per week), which limits interpretation of NPS burden. Examining the association between NPS symptom frequency and EF may provide additional prognostic clarity. Measurement of EF was limited to three neurocognitive subtests, which do not capture all aspects of EF. Modeling EF using a variety of measures tapping several subdomains of EF (e.g., planning, decision-making) is necessary for improving ecological validity of findings. Finally, while total NPS severity scores were used as a first step in our analyses, future research examining the role of individual NPS will allow for development of precise and targeted interventions.

Conclusions

In summary, older adults with ADRD exhibit significant decline in EF over four years, and this decline becomes more accelerated with higher NPS severity at early stages. Further, we identified thresholds of NPS severity that may be prognostic of anticipated cognitive change. Our results suggest that early assessment of NPS is important for predicting EF decline in MCI and dementia. Early evaluation of NPS may allow for identification of patients who are at higher risk for cognitive decline and offer the opportunity for early symptom management and intervention. Early treatment of NPS, regardless of the level of severity, should be prioritized to minimize EF decline and associated declines in independence.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1355617724000730.

Acknowledgements. The NACC database is funded by NIA/NIH Grant U24 AG072122. NACC data are contributed by the NIA-funded ADRCs: P30 AG062429 (PI James Brewer, MD, PhD), P30 AG066468 (PI Oscar Lopez, MD), P30 AG062421 (PI Bradley Hyman, MD, PhD), P30 AG066509 (PI Thomas Grabowski, MD), P30 AG066514 (PI Mary Sano, PhD), P30 AG066530 (PI Helena Chui, MD), P30 AG066507 (PI Marilyn Albert, PhD), P30 AG066444 (PI John Morris, MD), P30 AG066518 (PI Jeffrey Kaye, MD), P30 AG066512 (PI Thomas Wisniewski, MD), P30 AG066462 (PI Scott Small, MD), P30 AG072979 (PI David Wolk, MD), P30 AG072972 (PI Charles DeCarli, MD), P30 AG072976 (PI Andrew Saykin, PsyD), P30 AG072975 (PI David Bennett, MD), P30 AG072978 (PI Neil Kowall, MD), P30 AG072977 (PI Robert Vassar, PhD), P30 AG066519 (PI Frank LaFerla, PhD), P30 AG062677 (PI Ronald Petersen, MD, PhD), P30 AG079280 (PI Eric Reiman, MD), P30 AG062422 (PI Gil Rabinovici, MD), P30 AG066511 (PI Allan Levey, MD, PhD), P30 AG072946 (PI Linda Van Eldik, PhD), P30 AG062715 (PI Sanjay Asthana, MD, FRCP), P30 AG072973 (PI Russell Swerdlow, MD), P30 AG066506 (PI Todd Golde, MD, PhD), P30 AG066508 (PI Stephen Strittmatter, MD, PhD), P30 AG066515 (PI Victor Henderson, MD, MS), P30 AG072947 (PI Suzanne Craft, PhD), P30 AG072931 (PI Henry Paulson, MD, PhD), P30 AG066546 (PI Sudha Seshadri, MD), P20 AG068024 (PI Erik Roberson, MD, PhD), P20 AG068053 (PI Justin Miller, PhD), P20 AG068077 (PI Gary Rosenberg, MD), P20 AG068082 (PI Angela Jefferson, PhD), P30 AG072958 (PI Heather Whitson, MD), P30 AG072959 (PI James Leverenz, MD).

Funding statement. SEJ is supported by NIH/NIGMS P20GM109025 (Project R-2). The funding body had no role in the design of the study, analyses, interpretation of the data, and writing of the manuscript.

Competing interests. The authors report no conflicts of interest.

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https://doi.org/10.1017/S1355617724000730 Published online by Cambridge University Press