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RESEARCH ARTICLE

Differentiating traits and states identifies the importance of chronic neuropsychiatric symptoms for cognitive prognosis in mild dementia

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Abstract

Introduction: Neuropsychiatric symptoms (NPS) in dementia are associated with poor cognitive outcomes in longitudinal studies. Whether this is due to differences in symptom burden between persons (BP) or changes within persons (WP) is unknown.

Methods: Patients with mild Alzheimer's disease (AD, n = 111) and Lewy-body dementia (LBD, n = 85) were assessed annually for 8 years. We modelled the association between NPS assessed by the Neuropsychiatric Inventory (NPI) and Mini-Mental State Examinations (MMSE) using Tobit mixed-effects model with NPS as individual means over time (BP) and its deviance (WP).

Results: The association between higher NPS and poorer cognitive outcomes was mostly due to BP differences for the NPI-total score, and in particular for delusions, hallucinations, agitation, aberrant motor behavior, and apathy scores.

Discussion: The NPS trait (BP) effect on cognitive decline is considerably stronger than the state effect (WP). Clinically, long-term rather than episodic NPS better identifies patients with poor cognitive outcomes.

KEYWORDS
Alzheimer's disease, apathy, behavioral disturbances, between-person, chronic, cognitive decline, cognitive prognosis, dementia with Lewy bodies, dementia, MMSE decline, Neuropsychiatric Inventory, neuropsychiatric symptoms, psychosis, trait, within-person

1 | BACKGROUND

Cognitive trajectories in dementia differ markedly.[1] Identifying factors that explain prognostic differences is essential for clinical management and, potentially, to administer targeted interventions.[2] Neuropsychiatric symptoms (NPS) have consistently been associated with cognitive decline.[3,4] However, NPS follow complex trajectories with resolution and recurrence over time. NPS can manifest differently in patients with Alzheimer's disease (AD) compared to Lewy body dementia (LBD), with more psychotic symptoms in LBD.[5–9] Although the relationship between a higher burden of NPS and poor cognitive outcomes is well established, little is known regarding how the NPS variation over time affects the relationship with cognitive decline.

Over time, NPS could relate to cognition in several ways. For example, a psychotic episode could lead to reduced performance on a cognitive test during the acute episode, with no further effect on the cognitive trajectory once the symptom subsides. This could be described as a state effect. Another possibility is that psychosis is linked to a more rapid cognitive decline that lasts throughout the study, independent of its timing. For example, psychosis could signify more severe

HIGHLIGHTS

- Neuropsychiatric symptoms (NPS) fluctuate over time in mild dementia
- This fluctuation complicates the assessment of how NPS relate to cognition over time
- We distinguished each person's average NPS level from their fluctuations
- Chronic NPS have a much stronger impact on cognition than current NPS

RESEARCH IN CONTEXT

1. **Systematic review**: The literature was reviewed by the authors using traditional (i.e. PubMed) sources. Multiple longitudinal studies describe poor cognitive prognosis in dementia-patients with more neuropsychiatric symptoms (NPS). However, whether this relates to NPS differences between-persons (BP) or NPS changes within-persons (WP) has not been addressed. This could potentially lead to underestimation and a reduced understanding of the relationship.
2. **Interpretation**: Overall, taking into account the BP/WP distinction revealed a stronger association between NPS and cognitive decline compared to standard analysis. BP differences of the NPI-total were more strongly related to cognitive decline than WP changes.
3. **Future directions**: Our study shows that chronic levels of NPS are substantially more important for cognitive prognosis than current symptoms but would benefit from replication. Future longitudinal studies on the etiology or treatment of NPS may find new insights by focusing on patients with higher levels of chronic NPS.

neuropathology. This could be described as a trait effect. These possibilities are not mutually exclusive. Thus, a combination could be true.

Assessing the state and trait components of the relationship between NPS and cognitive decline can further the understanding of the clinical progression of dementia and could help identify treatment strategies that are more likely to be successful. However, assessing such longitudinal relationships requires specific statistical methods.[10] Multilevel and structural equation models can estimate both the between-person effect (BP, or trait) and the within-person effect (WP, or state) of time-varying covariates measured repeatedly over time in longitudinal studies.[11–14] However, without specific procedures, both WP and BP effects are assumed to be equal and summarized as a "convergent effect," which can lead to bias.[15]

We have previously shown the frequency and individual variations of NPS in dementia and overall association with cognition.[3,9] The aim of this study was to separate the BP and WP components of NPS of the associations with cognitive trajectories in patients with mild dementia due to AD and other dementias, and LBD.

2 | METHODS

2.1 | Study design

The Dementia Study of Western Norway (Demvest) is a longitudinal cohort study of patients referred to dementia clinics in Hordaland and Rogaland counties who had mild dementia. There are no other hospitals and none, or little, private health care for these patients. All general practitioners in the area were invited by letter to refer all patients with suspected dementia to reduce referral bias, as described previously.[9] All dementia diagnostic units (geriatric, neurology, and psychiatric) in the region recruited patients to the study. Further, all residents are covered by the same national insurance scheme with restricted co-payments. After screening 667 patients from unselected referrals, 244 were included. For this study, 222 patients with mild dementia had longitudinal Neuropsychiatric Inventory (NPI) measurements. The patients were classified as either Alzheimer's disease or other dementias (AD, n = 137) or LBD (n = 85). The group of patients with Alzheimer's disease or other dementias included 121 patients with AD, nine patients with mixed AD/vascular dementia, and seven patients with other dementias.

2.2 | Procedure

All patients with mild dementia were included from 2005 through 2007, and we continued to selectively recruit patients with LBD (ie, dementia with Lewy bodies and Parkinson's disease dementia), to enhance the number of patients in this group. Mild dementia was defined as a Mini-Mental State Examination (MMSE) score of at least 20 or Clinical Dementia Rating (CDR) global score of 1. The LBD cohort included 16 Parkinson's disease dementia and 69 with dementia with Lewy bodies. These patients were combined as there are no major differences between these diseases pathologically or in long-term follow-up reported.[16] Exclusion criteria were moderate or severe dementia, acute delirium at inclusion, previous bipolar disorder or psychotic disorder, or recently diagnosed major somatic illness. The definition of major somatic illness was one which, according to the clinician, would significantly impact cognition, function, or study participation. Clinicians followed restrictive national guidelines on the use of psychotropic medication.

Physical, neurological, and psychiatric assessments were performed annually, including the NPI and MMSE. At baseline, the assessment included a detailed neuropsychological test battery, routine blood and cerebrospinal fluid analyses, and brain magnetic resonance imaging. Dopamine transporter single-photon emission computed

tomography scans were available for most patients with suspected LBD. A consensus diagnosis was made in a three-members panel including two psychiatrists and one geriatrician using all data available after 5 years of follow-up. The panel members reached consensus for all participants. Pathological diagnosis was possible for 56 patients in the Demvest cohort, showing diagnostic accuracy above 80% for both AD and LBD.[17] The full clinical and diagnostic assessments are described in detail elsewhere.[18] After 8 years of follow-up, 35 patients were still in the study. Later follow-ups were excluded from analysis due to low numbers and severe floor effect on the MMSE (see below).

2.3 | Measures

The validated Norwegian 12-question NPI was administered to family or caregivers.[19,20] The 12 items were registered as present, and if present, scored according to their frequency (1–4) and severity (1–3), and we report the frequency X severity score for the individual items representing the prior 4 weeks. A total score was calculated by adding the 12 item scores (possible range 0–144). Due to the complex statistical distributions of these scores, binary scoring was applied at the established cut-off at ≥ 4, indicating clinical significance.[21,22] Euphoria was too rare to give enough statistical power for single-item analysis and was thus not considered.[9]

The validated Norwegian version of the MMSE (range 0–30) was used to measure cognition. The MMSE reliably detects cognitive change over observation periods above 3 years and correlates with pathological measures of disease severity.[23] However, floor effects are expected with progression to severe dementia and can lead to statistical bias if not handled by appropriate methods.[24,25]

2.4 | Statistics

A *P*-value <0.05 was considered significant. Intraclass correlation coefficients (ICCs) were derived from empty-means logistic or linear mixed effects models as an indicator of fluctuations versus stability. On a scale from 0 to 1, ICCs closer to 0 indicate more fluctuation (i.e., WP variation) and closer to 1 indicate stability (i.e., BP variation) with scores above or below 0.5 indicating whether WP or BP variation dominates. Longitudinal descriptive statistics for the binary NPS categories included BP variation (how many persons had at least one episode), WP variation (total symptomatic occasions in patients who had at least one episode). Of note, this descriptive method differs from the person-mean centering described below to analyze BP and WP effects.

The associations between NPS and cognitive decline were estimated in a multilevel model with the MMSE as the outcome and the square-root transformation of the NPI total, or NPI items as binary predictors, and time in study. We adjusted the model for age, sex, and diagnostic groups, and any significant interactions with time in study. Floor effects occur in longitudinal studies when patients reach and repeatedly score zero on the MMSE.[26] Floor effects will lead to an underestimation of cognitive decline. Accordingly, a Tobit mixed-effects model was used. We selected a quadratic trajectory for time with random intercepts and slopes and an unstructured variance-covariance matrix based on the Bayesian information criterion (BIC). Continuous predictors were mean-centered and continuous longitudinal predictors by their grand-mean (i.e., the NPI total). The time variable was left uncentered (zero at baseline). A model using the NPI scores without differentiating BP from WP (i.e., standard analysis) was performed first. This provided a fixed effect that represents a weighted summary of the BP and WP components, sometimes referred to as a convergence effect.

Next, we estimated separate fixed effects for the BP and WP components, allowing them to be unequal. The separate BP and WP fixed effects were estimated by first calculating the individual means of NPS symptoms over time (BP) and the occasion-specific deviance from the individual mean (WP). Both were then entered as predictors in the Tobit mixed-effects model described above. For the NPI total, the individual mean represents the average score for an individual over time. For the NPI items, the individual means represent the average probability of an individual having a symptom over the observed period. The individual means of the NPI scores were mean-centered so that the interpretation of the WP fixed effects indicates the impact on cognition from having "more or less symptoms than usual." Differences between BP and WP associations and respective interaction with time were tested by a Wald test.[27,28] Missing data were assumed to be missing at random as they were mostly due to death, predicted by age, sex, diagnostic groups, cognitive decline, and NPS, all in the model. For comparability, effect sizes in the multilevel models were standardized[29] after analysis for overall, BP and WP components as described for Tobit mixed-effects models.[30] For binary predictors, i.e. the NPI items, effect sizes were partially standardized. Please see the supplementary material, section 4.1, for details. Analyses were conducted first on all patients with mild dementia and according to the diagnostic groups of AD and other dementias compared to LBD using Stata 15.[31]

2.5 | Ethics

All participants and their legal representative signed informed consent. The study was approved by the regional ethics committee (2010/633) and the Norwegian authorities for collection of medical data and received financial support from the regional health authorities of western Norway, Helse-Vest. All data were handled and kept in accordance with national health- and data-privacy protocols.

3 | RESULTS

3.1 | Study participants and descriptive statistics

The characteristics of study participants are shown in Table 1. Patients were on average 75.3 years old when joining the study (standard deviation [SD] 7.4) and most (59%) were female. Comparing AD and other dementias to LBD, there was a female predominance in AD and other dementias (67%) not present in LBD (45%). Figure 1 lists the

TABLE 1 Characteristics of study participants

Baseline	All (N = 222)	ADOD[a] (N = 137)	LBD[b] (N = 85)
Age, mean [SD]	75.3 [7.4]	75.2 [7.8]	75.4 [6.9]
Female, %	59	67	45**
Longitudinal	MMSE, mean [SD], zero (%)[c]	NPI-total, mean [SD]	
BL (N = 222)	23.7 [2.7], (0.0)	19.7 [18.2]	
FU1 (N = 221)	21.3 [4.7], (0.5)	18.5 [17.9]	
FU2 (N = 186)	18.2 [6.4], (2.2)	20.2 [18.4]	
FU3 (N = 167)	15.3 [7.4], (4.8)	22.2 [18.9]	
FU4 (N = 138)	13.1 [8.1], (11.6)	21.8 [17.0]	
FU5 (N = 108)	10.1 [8.9], (22.2)	22.0 [17.5]	
FU6 (N = 73)	7.8 [9.4], (48.0)	28.7 [22.0]	
FU7 (N = 47)	8.7 [9.5], (42.6)	23.3 [16.9]	
FU8 (N = 35)	6.0 [8.1], (48.6)	22.8 [19.2]	

Abbreviations: ADOD, Alzheimer's disease and other dementias; FU, follow-up; LBD, Lewy body dementia; MMSE, Mini-Mental State Examination; NPI-total, Neuropsychiatric Inventory sum of all domain scores (domain score = frequency x intensity); SD, standard deviation.
[a]Includes 121 patients with AD, 9 patients with mixed AD/vascular dementia, and 7 patients with other dementias.
[b]Includes 69 patients with dementia with Lewy bodies and 16 patients with Parkinson's disease dementia.
[c]The number of patients scoring zero on the MMSE per occasion in percent of MMSE measurements, where higher percentages increases the risk of a floor effect.

attended follow-ups, missing data, cumulative deaths, and the change in study population over time. Missing data were predominantly due to death and 146 participants had died at the scheduled follow-up eight, which had 35 active participants. The remaining 41 participants could either not complete the examinations, had dropped out permanently, or missed follow-up eight. Over time, there was selection for survivors who were younger, had AD or other dementias, or were female (Figure 1).

The mean NPI-total score showed a complex non-linear trajectory. The NPI-total score had an ICC of 0.30 indicating predominant WP variation, that is, fluctuation within subjects. Depression, disinhibition, and sleep disturbances had ICCs 0.22 to 0.23 (Table S1 in supporting information). Delusions, anxiety, aberrant motor behavior, and sleep disturbances had ICCs of 0.38 to 0.39. Agitation (ICC 0.41), irritability (0.46), hallucinations (0.45), and apathy (0.60) fluctuated less and were thus more stable. The frequency and stability of NPS are reported in Tables S1 and S2 in supporting information, the latter by diagnostic group.

3.2 | The NPI total score and cognitive prognosis

Table 2 and Figure 2 show the results of the longitudinal analysis regarding the relationship between the total NPI and MMSE scores over time. The NPI-total score had a small but significant interaction with time indicating more rapid MMSE decline with higher NPI-total scores. The standardized fixed effect (sFE) was 0.04, $P = 0.006$, meaning a 0.04 SD increase in MMSE decline per year per 1 SD change in the square root of the NPI-total score (see Figure 2A). However, a modified Wald test showed that the BP and WP interactions with time were significantly different ($P < 0.001$, not in Table 2). The individual means, representing the BP variation, had a much stronger association with MMSE decline where one SD higher individual mean NPI total was associated with a −0.19 SD decline in MMSE per year (sFE −0.19, $P < .001$, Figure 2B). In contrast, the deviance scores, representing the WP variation, had a weaker association with poorer MMSE scores (sFE −0.09, $P < .001$) relative to the individual means. This association did not change significantly over time.

3.3 | Individual neuropsychiatric symptoms and cognitive prognosis

Table 3A shows the results of the longitudinal analyses for the NPI items, which were the most related to cognitive decline. From these, the overall, WP and BP components for selected NPI items are illustrated in Figure 3. These symptoms included delusions, hallucinations, agitation, apathy, and aberrant motor behavior. Hallucinations, agitation, and apathy had significant associations with MMSE score, but no interaction with time using the measured scores as predictors. Delusions and aberrant motor behavior were not significantly associated with MMSE score over time. Distinguishing the BP and WP components showed statistically stronger and significant interactions with time, that is, higher scores were associated with a more rapid cognitive decline for hallucinations and aberrant motor behavior. Among these symptoms, the only significant within-person component associated with MMSE was seen for agitation.

Table 3B shows that irritability, and disturbances in appetite, had significant associations with MMSE. However, the subsequent analysis found that this pertained only to the within-person components, none

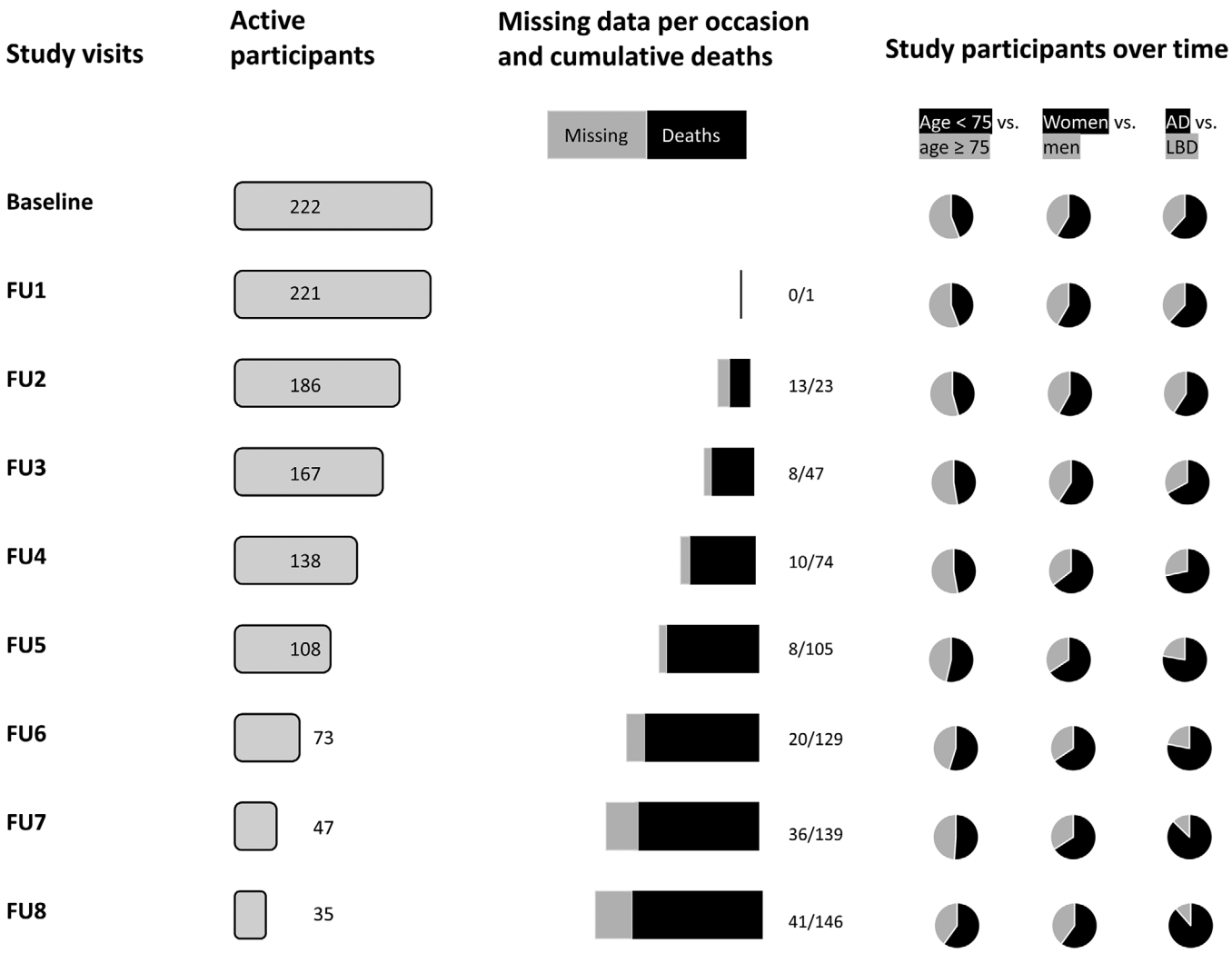

FIGURE 1 Study flowchart. The first column on the left lists the study visits, from baseline until follow-up (FU) eight. The second column lists the number of active participants at the visits. The third column lists the number of measurements missing (gray) relative to the 222 participants at baseline and the cumulative number of deaths (black). Missing data (gray) were due to a mixture of causes, including drop-out; severe illness; missed appointments; and at the later follow-ups, inability to perform testing. The fourth column listing three columns of circles shows pie charts of age groups, sex, and diagnostic groups. The AD group included Alzheimer's disease (AD; n = 121), mixed AD/vascular (n = 9), and other causes of dementia, whereas the LBD group includes dementia with Lewy bodies (LBD; n = 69) and Parkinson's disease dementia (n = 16). Overall, one can see selection of younger, female patients with AD or other dementias over time with fewer older, male and LBD patients

of which interacted with time. Table 3C shows that anxiety, depression, disinhibition, and sleep disturbances had no significant associations with cognition.

3.4 | NPS and cognition in AD and other dementias compared to LBD

The individual means of the NPI-total score, delusions, hallucinations, and aberrant motor behavior had stronger associations with MMSE decline in LBD compared to AD and other dementias, but these differences were not significant (Table S3 in supporting information). Interestingly, only the individual means of apathy showed a significant difference by diagnostic groups, that is, an association with MMSE was found in LBD but not in AD and other dementias (Figure 4).

4 | DISCUSSION

This study aimed to investigate the association between NPS and cognition in patients with mild dementia who were followed annually for up to 8 years. We corroborate previous reports of an association between more NPS and more rapid cognitive decline. For the first time, we demonstrate the critical importance of patients who have on average high levels of NPS over time (i.e., BP component) in contrast to a relatively minor impact of fluctuations (WP) in NPS, even as NPS vary considerably over time. Studying specific NPS identified similar

TABLE 2 Total score of neuropsychiatric symptoms and cognition prognosis in dementia

	NPI-total				BP and WP NPI-total			
	sFE	FE	95% CI	*P*	sFE	Est	95% CI	*P*
Age	−0.07	−0.09	[−0.15, −0.03]	.005*	−0.07	−0.08	[−0.14, −0.02]	.007*
Age x time	0.19	0.10	[0.04, 0.15]	.001*	0.19	0.10	[0.04, 0.15]	.001*
Age x time^2	−0.06	−0.01	[−0.02, −0.01]	<.001**	−0.06	−0.01	[−0.02, −0.01]	<.001**
Female	−0.01	−0.10	[−0.96, 0.75]	.758	−0.1	−0.09	[−0.09, 0.74]	.831
Time	−0.58	−2.27	[−2.83, −1.71]	<.001**	−0.58	−2.24	[−2.79, −1.70]	<.001**
Time^2	−0.12	−0.19	[−0.24, −0.15]	<.001**	−0.13	−0.20	[−0.27, −0.16]	<.001**
LBD	0.02	0.19	[−0.68, 1.07]	.721	0.03	0.25	[−0.62, 1.13]	.573
LBD x time	−0.23	−0.92	[1.66, −0.17]	.016*	−0.21	−0.81	[−1.54, −0.09]	.028*
√(NPI−total)								
Score[a]	−0.02	−0.07	[−0.22, 0.08]	.682				
Score x time	−0.04	−0.07	[−0.13, −0.02]	.006*				
BP[b]					−0.02	−0.10	[−0.38, 0.19]	.512
BP*time					−0.19	−0.54	[−0.79, −0.30]	<.001**
WP[c]					−0.09	−0.25	[−0.37, −0.12]	<.001**

Abbreviations: BP, between persons; CI, confidence interval; FE, fixed effects; LBD, Lewy body dementia; SD, standard deviation; sFE, standardized fixed effects; WP, within persons.

Age centered at 70. Scales of NPI variables listed below, of which a and b are centered in the model:

[a]Square root transformation of NPI−total: mean 4.08, SD 2.12, range 0 to 10.4.

[b]Individual−mean after transformation: mean 4.09, SD 1.37, range 0 to 8.2.

[c]Deviance score from individual mean: −0.00, SD 1.61, range −6.0 to 6.4.

findings. Our findings suggest that separating BP and WP effects of NPS is crucial to estimate the longitudinal association between NPS and cognition.

The relatively larger impact of the calculated individual means compared to using the NPS total score (and similarly so for the individual items) is due to a well-known statistical phenomenon that can lead to underestimation in mixed-effects models. Time-varying covariates in multilevel models vary between (level two) and within persons (level one). Still, the model generates only one fixed effect, referred to as a convergence effect in this setting. The convergent effect is a weighted estimate of the BP and WP components. However, issues related to the model estimation often skew the size of the convergence effect toward the within-person effect (including any interactions).[32] This description fits very well with our findings. Only the BP component had a significant interaction with time. This interaction was likely masked by the absence of an interaction between time and the WP component. The NPI total score had an ICC of 0.30, indicating that 70% of the variability occurs in individuals over time (i.e., fluctuations). Consequently, only 30% of the variability is due to differences between individuals, which was most associated with cognitive outcomes. Indeed, change over time was the primary source of variability for all NPI items except apathy, which had an ICC > 0.50, indicating predominant BP variation.

Several studies have shown an association between NPS and cognition. Still, studies have also demonstrated a lack of association or inverse association, especially in mid- to late dementia.[5,8,33] Compared to our study, many studies were short term or suffered from higher attrition. Importantly, a separation between the BP and WP associations was not performed. Such analyses, also in existing cohorts, could confirm whether the impact of NPS on cognitive prognosis in dementia has been considerably underestimated due to a lack of differentiation between the BP and WP components. Our findings indicate that the BP component of NPS is substantially more important for cognitive prognosis and underlines the importance of long-term management and prevention of NPS. In clinicopathological studies, it is common to follow patients over time and link the last measurement or fit a longitudinal model to the pathological processes in the *post mortem* brain as cognitive decline is closely correlated to neuropathological processes.[34] Our data suggest that the individual means of NPS over time could be worth examining as potentially more closely correlated to neuropathological processes in future studies. However, whether a reduction in NPS would cause an improvement in cognitive function in dementia is not known. In a theoretical scenario in which reducing NPS would improve cognition, our data suggest that treating NPS only when they are more severe than usual would be expected to have only a small effect on cognition. Detecting small effects needs considerably larger sample sizes. Our findings support targeting patients with severe NPS for long-term intervention and possible larger preventive intervention schemes.

Differences in individual means rather than having more symptoms than usual were more associated with cognitive decline for the items hallucinations, delusions, agitation, apathy, and aberrant motor behavior. Overall, our results are in line with reviews and previous studies classifying psychotic and hyperactivity symptoms most strongly associated with cognitive decline.[5,11,13,35] Similarly, apathy has been linked to poor cognitive outcomes in multiple studies.[36] However, previous

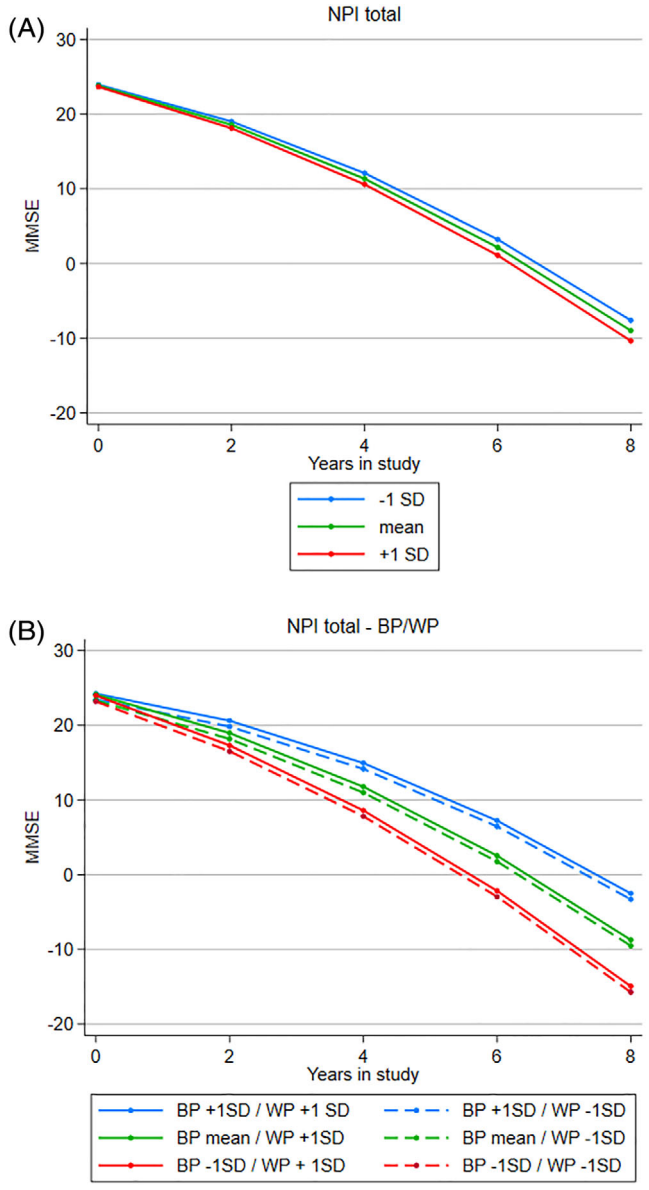

FIGURE 2 The Neuropsychiatric Inventory (NPI) total score and cognitive prognosis. The upper trajectory (A) illustrates the predicted Mini-Mental State Examination (MMSE) scores at ±1 standard deviation (SD) from the mean of the NPI-total score. In comparison, the differences in MMSE trajectories are larger using the between-person (BP) NPI-total score (B), calculated as the mean of each individual over the occasions they were observed. The within-person effects (calculated as the deviance from the individual means) are much weaker, note that they indicate +1 SD (solid line) and −1 SD (stippled line), which should be compared to the blue and red color lines of the BP effect. Note that the within-person effect indicates a difference of 2 SD between the lines for visibility compared to 1 SD difference between the colored lines

studies have to our knowledge not distinguished between the WP and BP components of NPS measured over time. The importance of particularly aberrant motor behavior may have been missed in studies and meta-analyses if aberrant motor behavior, in general, has only BP associations with cognitive decline, as in our study.

The comparisons between AD and other dementias and LBD must be considered purely exploratory, as this analysis was underpowered considering the complex statistical models. Overall, a high chronic burden of the NPI total and several individual items could seem to be worse for cognitive outcomes in LBD compared to AD and other dementias. However, the difference was only significant for apathy, suggesting that persistent apathy could be a candidate marker of worse cognitive outcomes in LBD but not in the group of AD and other dementias.[3] Such differences between diagnostic groups could be important for the treatment and management of NPS not only in dementia, as apathy is also a key symptom in Parkinson's disease.

Irritability and disturbances in appetite showed only weak WP associations (i.e., individual fluctuations) with cognition, perhaps not clinically meaningful. Previous studies have shown large variability in the association between irritability and cognitive outcomes in dementia.[5] There are few longitudinal studies assessing disturbances in appetite in dementia. Perhaps being irritable or having insufficient nutrient intake affects motivation for cognitive testing.

Depression is often suggested as important for cognitive decline in both dementia and mild cognitive impairment, but had no significant association with cognitive decline in our data. In line with our findings, several of the more long-term studies have shown conflicting or negative results regarding the impact of depression on cognitive outcomes with established dementia. In contrast, depression has consistently been associated with increased risk of dementia.[5] Perhaps more significantly, the NPI applies a simplified definition of depression.[37]

Strengths of the study include the extended follow-up time, structured assessments, and high completeness of data in survivors.[17] There are limitations. We do not have structured information regarding non-pharmacological interventions, but the centers followed restrictive national guidelines on psychotropic use. We cannot exclude referral bias from primary care patients. Patients with LBD had higher mortality, and thus there was a considerable selection for patients with AD and other dementias over time. There was also a selection of younger patients, and somewhat for females. For these observed covariates, the mixed-effects model should appropriately adjust the results under the missing at random assumption, which assumes that the missing data can be predicted by the observed data.[32] However, unobserved patient characteristics could exist and could bias the results. Whether this has occurred cannot readily be tested. A joint model could have been used to guard against bias related to unobserved missing data. Still, no joint model that can also handle floor effects is currently implemented in standard statistical software. Furthermore, the estimated latent trajectories after the floor effect can be verified. We have used the individual mean and its deviance as measures of BP and WP effects and adjusted for time in the models, as the NPI-total and some NPS increase somewhat over time although they mostly fluctuate. Whether other methods could be superior for time-varying covariates that change over time when time is adjusted for is a matter of debate.[10] The comparison between diagnostic groups was limited by heterogeneous subgroups.

In conclusion, even as NPS predominantly fluctuates over time, high levels of NPS sustained over time have the most negative impact on cognitive prognosis in dementia. Clinically, the magnitude of the effect

TABLE 3 Individual neuropsychiatric symptoms and cognitive prognosis in dementia

		Intercept[c]				Slope[d]			
NPS[a]	A[b]	sFE	FE	95% CI	*P*	sFE	FE	95% CI	*P*
A. NPS with predominant between–person association with MMSE decline									
DEL		−0.02	−0.58	[−1.20, 0.05]	.071	—	—	—	—
	BP	−0.03	−1.36	[−2.94, 0.23]	.094	−0.12	−2.05	[−3.85, -0.25]	.025*
	WP	−0.01	−0.43	[−1.10, 0.24]	.206	—	—	—	—
HAL		−0.08	−0.75	[−1.41, −0.09]	.025*	—	—	—	—
	BP	−0.01	−0.32	[−2.21, 1.52]	.719	−0.17	−2.81	[−4.46, −1.15]	.001*
	WP	−0.02	−0.68	[−1.36, 0.01]	.052	—	—	—	—
AGI		−0.09	−0.89	[−1.51, -0.28]	.004*	—	—	—	—
	BP	−0.03	−1.24	[−2.89, 0.40]	.138	−0.12	−2.10	[−3.57, −0.64]	.005*
	WP	−0.03	−0.77	[−1.40, −0.12]	.019*	—	—	—	—
APA		−0.06	−0.54	[−0.97, −0.11]	.014*	—	—	—	—
	BP	−0.05	−1.53	[−2.89, −0.16]	.028*	−0.10	−1.38	[−2.62, −0.14]	.029*
	WP	−0.02	−0.41	[−0.86, 0.05]	.080	—	—	—	—
AMB		−0.03	−0.25	[-0.76, 0.25]	.326		—	—	
	BP	−0.02	−0.82	[−2.44, 0.80]	.322	−0.17	−2.59	[−3.99, −1.18]	<.001**
	WP	−0.01	−0.15	[−0.67, 0.37]	.582	—	—	—	—
B. NPS with only within-person association with MMSE performance									
IRR		−0.07	−0.67	[−1.20, −0.14]	.014*	—	—	—	—
	BP	−0.03	−0.98	[−2.49, 0.53]	.202	—	—	—	—
	WP	−0.02	−0.63	[−1.20, −0.06]	.030*	—	—	—	—
APP		−0.06	−0.61	[−1.10, −0.12]	.015*	—	—	—	—
	BP	−0.03	−1.25	[−2.96, 0.45]	.148	—	—	—	—
	WP	−0.02	−0.55	[−1.06, −0.04]	.035*	—	—	—	—
C. NPS with no significant association with MMSE									
ANX		−0.04	−0.38	[−0.95, −0.20]	.202	—	—	—	—
	BP	0.02	0.84	[−0.88, 2.55]	.340	—	—	—	—
	WP	−0.02	−0.52	[−1.12, 0.09]	.094	—	—	—	—
DEP		−0.01	−0.07	[−0.56, 0.42]	.778	—	—	—	—
	BP	0.01	0.04	[−1.65, 1.73]	.964	—	—	—	—
	WP	−0.01	−0.08	[−0.59, 0.43]	.759	—	—	—	—
DIS		−0.04	−0.33	[−1.00, 0.35]	.337	—	—	—	—
	BP	−0.02	−1.04	[−2.79, 0.70]	.241	—	—	—	—
	WP	−0.01	−0.24	[−0.95, 0.47]	.513	—	—	—	—
SLE		−0.04	−0.39	[−0.93, 0.16]	.162	—	—	—	—
	BP	0.02	0.63	[−0.86, 2.13]	.406	—	—	—	—
	WP	−0.02	−0.55	[−1.13, 0.04]	.066	—	—	—	—

Abbreviations: CI, confidence interval; FE, fixed effects; sFE, standardized fixed effect.

[a]Neuropsychiatric symptoms (NPS): DEL, delusions; HAL, hallucinations; DEP, depression; ANX, anxiety; APA, apathy; AGI, agitation; IRR, irritability; DIS, disinhibition; AMB, aberrant motor behavior; SLE, sleep; APP, appetite.

[b]Analyses: Domain score ≥ 4 (empty cell); BP, between-person: association between individual mean and MMSE; WP, within-person: association between deviance score and MMSE.

[c]The association of NPS with the MMSE intercept (baseline level)

[d]The association of NPS with the slope, i.e., annual rate of change.

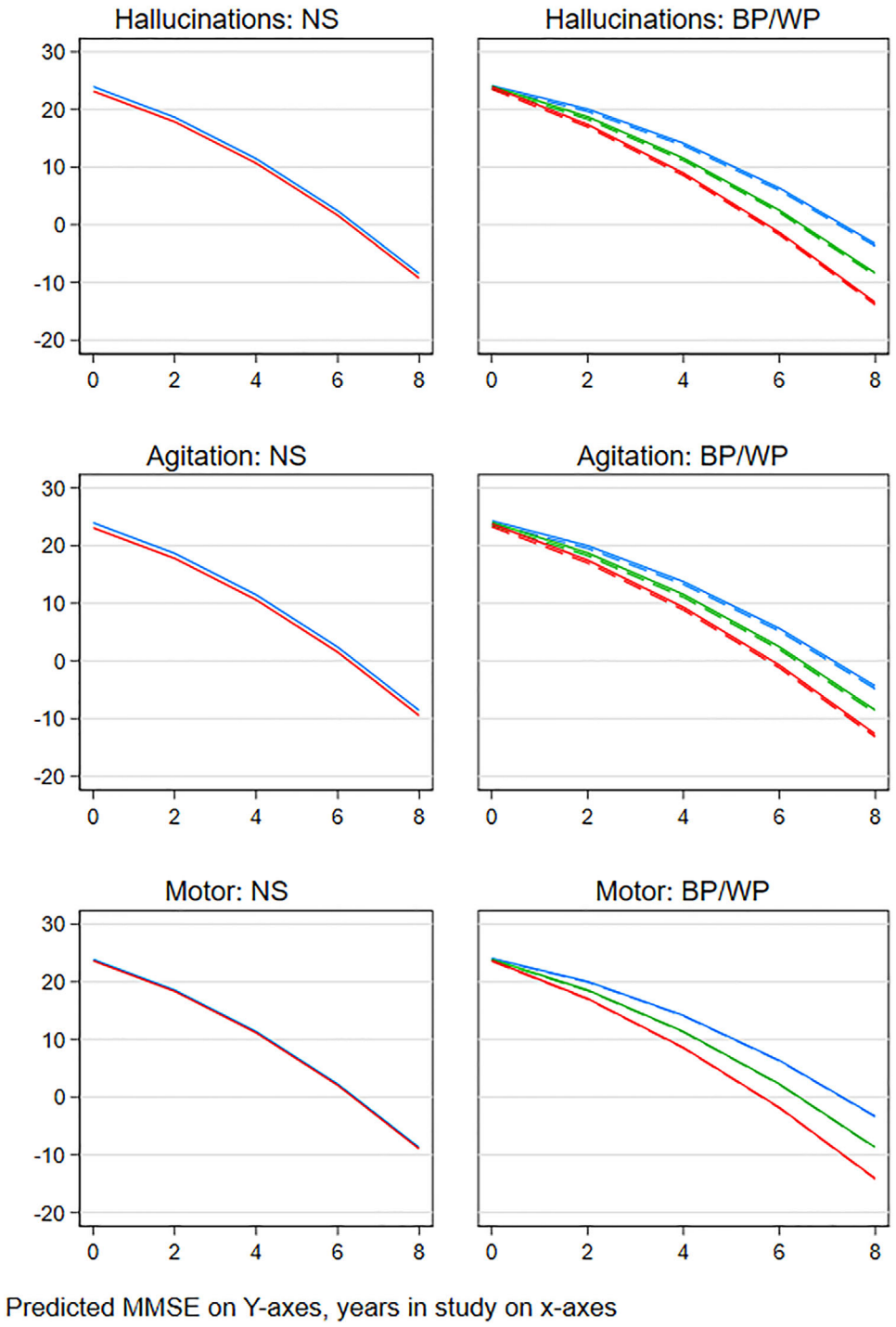

FIGURE 3 Individual neuropsychiatric symptoms and cognitive prognosis. Separating the between-person (BP) and within-person (WP) parts of the association between Neuropsychiatric Inventory (NPI) items and Mini-Mental State Examination (MMSE) score, reveals that the between-person differences (color indicates means ± 1 standard deviation [SD]) are considerably stronger than what is seen with the NPI score (NS, here a domain score above or equal to four) and the within-person associations (insignificant for hallucinations and aberrant motor behavior [motor, indicated by solid (+1 SD) and stippled (−1 SD) lines]). Note that the within-person effect indicates a difference of 2 SD between the lines for visibility compared to 1 SD difference between the colored lines

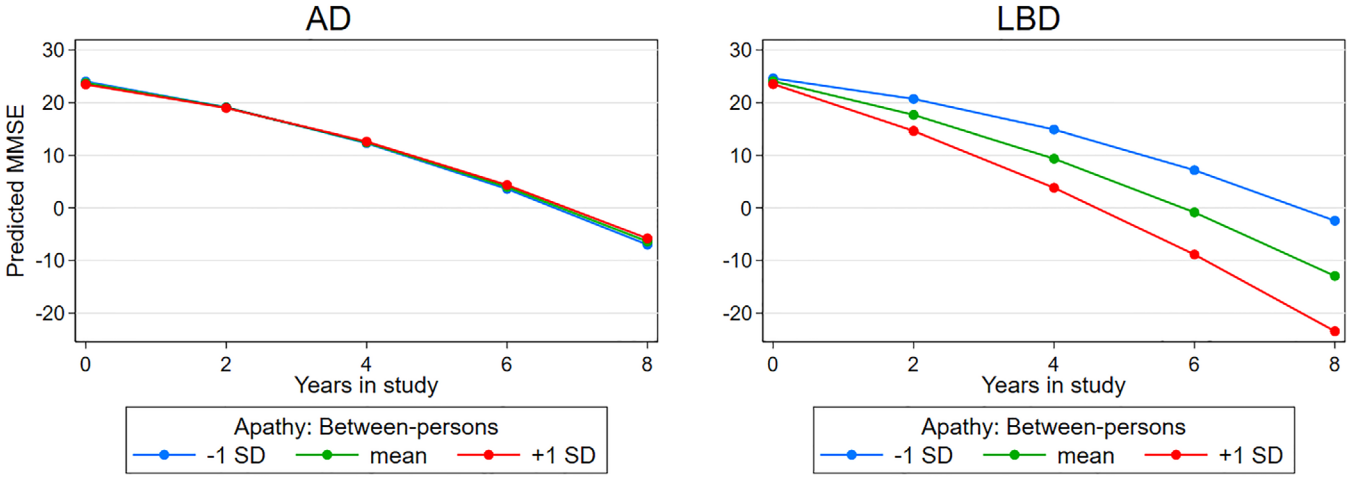

FIGURE 4 Apathy and cognitive prognosis in Alzheimer's disease (AD) and other dementias compared to Lewy body dementia (LBD). Only the between-person association is shown (The regular NPI score and the calculated within-person person scores had minimal associations with cognition in both groups). This post hoc analysis shows that chronic apathy has no impact on cognitive prognosis in AD but a considerable impact on cognitive prognosis in LBD. Abbreviations: MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; SD, standard deviation

of chronic NPS on cognitive progression is clinically meaningful. Hopefully, this vulnerable group could, to a more considerable extent, be targeted for long-term interventions to reduce NPS, which may be of benefit for their cognitive progression.

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CONFLICTS OF INTEREST

Audun Osland Vik-Mo and Lasse M. Giil declare that they have no conflict of interest. Dag Aarsland has received research support and/or honoraria from Astra-Zeneca, H. Lundbeck, Novartis Pharmaceuticals, and GE Health and serves as paid consultant for H. Lundbeck, Eisai, and Axovant.

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SUPPORTING INFORMATION

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