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Neuropsychiatric symptoms as a sign of small vessel disease progression in cognitive impairment

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ABSTRACT

Background: Neuropsychiatric symptoms associate cross-sectionally with cerebral small vessel disease but it is not clear whether these symptoms could act as early clinical markers of small vessel disease progression. We investigated whether longitudinal change in Neuropsychiatric Inventory (NPI) scores associated with white matter hyperintensity (WMH) progression in a memory clinic population.

Material and methods: We included participants from the prospective Sunnybrook Dementia Study with Alzheimer's disease and vascular subtypes of mild cognitive impairment and dementia with two MRI and ≥ 1 NPI. We conducted linear mixed-effects analyses, adjusting for age, atrophy, vascular risk factors, cognition, function, and interscan interval.

Results: At baseline (n=124), greater atrophy, age, vascular risk factors and total NPI score were associated with higher baseline WMH volume, while longitudinally, all but vascular risk factors were associated. Change in total NPI score was associated with change in WMH volume, $\chi 2 = 7.18$, $p = 0.007$, whereby a one-point change in NPI score from baseline to follow-up was associated with a 0.0017 change in normalized WMH volume [expressed as cube root of (WMH volume cm^3 as % intracranial volume)], after adjusting for age, atrophy, vascular risk factors and interscan interval.

Conclusions: In memory clinic patients, WMH progression over 1–2 years associated with worsening neuropsychiatric symptoms, while WMH volume remained unchanged in those with stable NPI scores in this population with low background WMH burden.

1. Introduction

Cerebral small vessel disease (SVD) causes 25% of ischaemic strokes and is a major contributor to cognitive impairment [1,2], including both vascular and Alzheimer's disease (AD) subtypes [2–4]. It is characterised by dysfunctioning perforating arterioles, capillaries, venules, and consequent damage to the brain parenchyma, and key radiological features include white matter hyperintensities (WMH) [5]. SVD progresses in many [6] but there is no specific treatment available yet. It is possible that SVD could be clinically detectable earlier, before it causes stroke or cognitive decline, and this could have implications for future SVD treatment trials.

Neuropsychiatric symptoms are common in patients with age-related cognitive impairment including Alzheimer's disease [7], post-stroke [8], and form part of the cognitive and behavioral syndrome of subcortical ischaemic vascular dementia [9]. Cross-sectional links between neuropsychiatric symptoms and SVD are established: more severe WMH are associated with apathy, fatigue, and delirium [10]. A more global measure of neuropsychiatric symptom burden, the total Neuropsychiatric Inventory (NPI) score [11], has been associated with SVD in some [12,13], but not all [14,15], cross-sectional studies, with inconsistencies arising from differences in sample sizes, populations, analysis methods, and outcome reporting across studies [10].

Longitudinal studies are sparse but are required to assess trajectories

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of both WMH and neuropsychiatric symptoms, allowing us to interpret relationships more robustly, since worsening neuropsychiatric symptoms could act as an earlier clinical detector of WMH progression. See Table A1, Supplementary Material for characteristics of published longitudinal studies assessing WMH and NPI.

In a memory clinic population with cognitive impairment due to Alzheimer's or vascular pathology, we aimed to identify (a) whether there is an intra-individual longitudinal association between change in WMH volumes and NPI scores between two time-points and (b) whether longitudinal change in neuropsychiatric symptoms, cognition or function best predicts WMH change between two time-points.

2. Material and methods

2.1. Participants

We analysed data collected by the Sunnybrook Dementia Study, a prospective cohort study at the Sunnybrook Health Sciences Centre, Toronto, Canada (ClinicalTrials.gov: NCT01800214). This ongoing study (1995-present, current analysis 1998–2018) recruited patients attending the outpatient memory clinic and included individuals with a diagnosis of neurodegenerative or vascular cognitive disorders, aged 40–90 years old with MMSE $\geq$ 16 and $\geq$ 8 years of education, who were fluent in English. The present analysis only included patients with mild cognitive impairment or dementia thought to be caused by AD, cerebrovascular disease, or a combination thereof, based on relevant criteria: National Institute on Aging - Alzheimer's Association criteria [16] and Diagnostic and Statistical Manual of Mental Disorders-IV [17] for probable or possible AD, vascular cognitive disorders criteria [18–20] for possible or probable vascular Mild Cognitive Impairment or vascular dementia, and mixed cognitive impairment according to possible coexisting cerebrovascular disease [19–22]. Study participants were excluded if there was evidence of a comorbid neurological or psychiatric illness other than stroke, history of head trauma, substance abuse, tumours, history of major psychiatric disorder (e.g. depression, schizophrenia, substance abuse/dependence), major systemic illness, current cancer treatment, and/or contraindication to MRI. The present analysis additionally excluded individuals with frontotemporal dementia, Parkinson's disease dementia, Lewy Body dementia, traumatic brain injury, individuals who did not attend follow-up brain MRI, and whose informants did not complete NPI at baseline.

2.2. Standard protocol approvals, registrations, and patient consents

The study was granted ethical approval by the Sunnybrook Research Ethics Board (reference 009–1998). All participants/caregivers gave written informed consent. All assessments were carried out in accordance with relevant guidelines and regulations.

2.3. Assessments

2.3.1. Informant-reported measures

The NPI is a 12-item informant questionnaire validated for use in cognitively impaired populations including mild impairment [23], assessing changes in 12 behavioral symptoms occurring within the past month which are new since the onset of cognitive impairment. It assesses agitation, anxiety, apathy, appetite change, aberrant motor behavior, delusions, depression, disinhibition, euphoria, hallucinations, irritability, and nocturnal behavior disturbance, with subscores assigned to each symptom, based on *frequency X severity*, resulting in a maximum score of 12 points per symptom. Individual symptom scores are summed to calculate the total NPI score, where the higher the score the worse the symptoms. NPI was performed within 3 months of MRI at both visits. Informants also completed the Cornell depression score which has been validated in both dementia and non-dementia populations [24], and the Disability Assessment for Dementia (DAD), a measure of functional status [25]. A DAD score of 100% indicates no disability.

2.3.2. Clinical and cognitive status

Baseline age, sex, years of education, vascular risk factors (hypertension, hyperlipidaemia, smoking status, and diabetes mellitus), and interscan interval were recorded. The presence or absence of vascular risk factors was ascertained from the medical records based on the most up to date criteria at the time of assessment. At both study visits, participants performed the Mini-Mental State Examination (MMSE) [26].

2.4. Magnetic resonance imaging

2.4.1. MRI acquisition

All participants were scanned at baseline and follow-up with a 1.5 T MRI (General Electric Signa, Milwaukee, WI) with the following protocol: a T1-weighted axial 3D Spoiled Gradient Recalled Echo (SPGR): repetition time (TR) = 35 ms, echo time (TE) = 5 ms, Number of Excitations (NEX) = 1, 35° flip angle, 22 × 16.5 cm field of view(FoV), 0.86 × 0.86 mm in-plane resolution, 1.2 to 1.4 mm slice thickness depending on head size, and an interleaved proton density (PD) and T2-weighted (axial dual-echo spin echo PD/T2): TE = 30/80 ms, TR = 3000 ms, NEX = 0.5, 20 × 20 cm FoV, 0.78 × 0.78 mm in-plane resolution, 3 mm slice thickness).

2.4.2. MRI processing

Brain tissue volumes were acquired using in-house validated semi-automatic pipelines described previously [27–30]. PD/T2 images were co-registered to T1 images to quantify gray matter (GM), white matter (WM), cerebrospinal fluid (CSF), supra-tentorial total intracranial volumes (ICV) and baseline and follow-up WMH volumes. Baseline whole brain atrophy was assessed using the brain parenchymal fraction (BPF), calculated as normal-appearing white matter + normal-appearing gray matter)/ICV.

2.5. Statistical analysis

We assessed differences between participants with MRI at baseline and follow-up (the present analysis) vs. those without follow-up MRI, to check for attrition bias (See Table A2, Supplementary Material). In figures, but not in statistical analysis, we present WMH volume change by quintiles. We transformed WMH volumes using the cube root of the WMH volume expressed as % ICV as this improved model fit, described in previous WMH linear mixed-effects models [31]. All references to WMH volumes, unless otherwise stated, describe normalized WMH measurements.

We summated a composite vascular risk factor score containing hypertension, hyperlipidaemia, diabetes and smoking status, described previously [32], to maximize the inclusion of confounders in the model and avoid overfitting.

We performed repeated-measures correlations of baseline and follow-up NPI symptom scores with baseline and follow-up WMH volumes (rmcorr package, R), adjusted for total intracranial volume. We used a linear mixed-effects model with a random effect for intercept across individuals to examine the associations between intra-individual longitudinal WMH volumes and total NPI scores, adjusting for age, interscan interval, atrophy (via BPF), and vascular risk factor score (lme4 package, R). We ran a second model to assess associations between WMH volumes, age, atrophy, functional (DAD), MMSE, and total NPI scores. We compared these models with null models that excluded the total NPI scores, using the likelihood ratio test. Sixteen participants did not have follow-up NPI but linear mixed-effects analysis includes participants with both complete and partial data [33]. We used R version 3.5.3.

Eight participants did not have available vascular risk factor data. Sensitivity analyses allocating maximum vs. minimum vascular risk factor scores to these participants produced similar estimates to results

reported here (See Table A3, Supplementary Material).

2.6. Data availability

Anonymized data not published within this article can be made available by request from the corresponding author.

3. Results

3.1. Baseline population characteristics

We included 124 participants who completed baseline and follow-up MRI in this analysis. Of 347 meeting diagnostic criteria for inclusion with completed NPI, 223 did not attend follow-up MRI: these individuals were older, scoring a mean of one point lower on baseline MMSE, with no differences in sex, functional status, or depression scores. After adjusting for sex and MMSE, the age difference between groups was not statistically significant (See Table A2, Supplementary Material).

Table 1 shows participant baseline characteristics. The 124 included participants predominantly had AD dementia or AD MCI (83%). The mean age was 69.8 years (SD ± 9.37) and 76/124 (61.3%) were female. Participants had mean 13.68 (SD ± 3.22) years of education and mean baseline MMSE score of 24.78 (SD ± 3.25). Fourteen (11.3%) had mild cognitive impairment and 110 (88.7%) had dementia.

Table 1
Baseline characteristics *n*=124. Mean (SD) Median (IQR).

Demographic, functional, cognitive factors	
Age, mean (SD)	69.8 (9.37)
Female	76 (61.3%)
Years of education, mean (SD)	13.68 (3.22)
Alzheimer's Disease (MCI or dementia)	103 (83%)
Vascular cognitive impairment incl. mixed VaD/AD	21 (17%)
Baseline MMSE score, mean (SD)	24.78 (3.25)
Follow-up MMSE score, mean (SD)	23.00 (5.48)
Cornell depression score, median (IQR)	5.00 (2–10)
Baseline NPI total score, median (IQR)	7 (2–15)
Follow-up NPI total score, median (IQR)	7 (3–16.5)
Baseline Disability Assessment for Dementia %, median (IQR)	89 (74–98)
Follow-up DAD %, median (IQR)	77.4 (54 – 91)
Interscan interval (months), median (IQR)	15 (13–24)
Inter-NPI interval (months), median (IQR)	15 (13–25)
Systolic BP (mmHg), mean (SD)	141.59 (18.91)
Diastolic BP (mmHg), mean (SD)	79.79 (10.51)
Vascular risk factors*	
Hypertension	53 (42.7%)
Hyperlipidemia	42 (33.9%)
Diabetes	7 (5.6%)
Current or former smoker	48 (38.7%)
Composite VRF score, median (IQR)	1 (0–2)
Imaging variables	
Total intracranial volume (mL), mean, (SD)	1195 (131)
Baseline WMH (mL),† median (IQR)	3.71 (1.01 – 13.65)
Follow-Up WMH (mL),† median (IQR)	3.99 (1.33 – 15.2)
WMH change (mL),† median (IQR)	0.55 (-0.17 – 2.0)
Brain Parenchymal Fraction, mean (SD)	0.74 (0.047)
Baseline WMH volume %ICV, median (IQR)	0.3 (0.087 – 1.12)
Baseline normalized WMH (cubed root as %ICV), mean (SD)	0.74 (0.35)

Note: * *n*=8 missing VRFs
see sensitivity analysis in Supplement † = Raw values. Abbreviations: SD = Standard deviation
IQR = Interquartile range
MCI = Mild cognitive impairment
VaD = vascular dementia
AD = Alzheimer's disease
MMSE = mini-mental state examination
NPI = Neuropsychiatric Inventory
DAD = Disability Assessment for Dementia
BP = blood pressure
VRF = vascular risk factors
WMH = white matter hyperintensities
ICV = intracranial volume

3.2. Description of longitudinal change in WMH volumes and neuropsychiatric symptoms

The median baseline WMH volume was 3.71 mL (IQR 1.01–13.65 mL) [i.e., 0.3% (IQR 0.08–1.12) of ICV]. The median interscan interval was 15 (IQR 13–24) months and the median follow-up WMH volume was 3.99 mL (IQR 1.33–15.2).

WMH volumes increased in 86/124 (69.3%) participants between time-points. The greatest WMH volume increases occurred in those with the highest baseline WMH volumes (Fig. 1a). NPI scores increased in 48 (38.7%) (Fig. 1b), decreased or remained unchanged in 61 (49.2%), no longitudinal data in 15 (12.1%). MMSE scores decreased in 65 (52.4%), increased/unchanged in 56 (45.2%), no longitudinal data in three (2.4%). Functional status declined in 78 (62.9%), improved/unchanged in 30 (24.2%), no longitudinal data in 16 (12.9%) participants.

The most prevalent neuropsychiatric symptoms at baseline were apathy (47.6%), depression (41.9%), agitation (32.3%) and irritability (36.3%), while at follow-up, apathy (56.9%), depression (39.4%), anxiety (32.1%) and night-time behavior change (30.3%) were most prevalent, with the greatest relative increases seen for prevalence of apathy (9.3%), anxiety (5.5%) and night-time behavior change (5.3%) (Fig. 2).

Repeated-measures correlations adjusted for total intracranial volume showed strongest associations between longitudinal WMH volumes and total NPI scores, depression, and night-time behavior change subscores (Table A4, Supplementary Material).

3.3. Worsening neuropsychiatric symptoms and WMH progression

On multivariable cross-sectional analysis, greater age, atrophy, vascular risk factors and total NPI score were associated with higher baseline WMH volume (Table 2a, Fig. A1, Supplementary Material) while longitudinally, the association with vascular risk factors did not remain (Table 2b). We found strong associations between longitudinal total NPI scores and normalized WMH volumes, $\chi^2 = 5.66$, $P = 0.017$, whereby a one-point increase in NPI scores from baseline to follow-up was associated with a 0.0015 increase in WMH [expressed as cube root of (WMH volume mL expressed as % ICV)], after adjusting for age, brain atrophy, vascular risk factors and interscan interval (Fig. 3, Table 2).

3.4. Worsening neuropsychiatric symptoms and WMH progression, adjusting for cognition and function

Cross-sectionally, baseline WMH volume associated more strongly with higher baseline NPI than MMSE or function (Table 3a, Fig. A2, Supplementary Material). Assessing longitudinal total NPI, MMSE, and functional status scores (DAD) together, bi-directional NPI change remained more strongly associated with longitudinal normalized WMH change than changes in MMSE or function, $\chi^2 = 6.03$, $P = 0.014$. (Table 3b). WMH increase was associated with increasing NPI and WMH decrease was associated with decreasing NPI, while MMSE/function did not significantly associate with either WMH increase or decrease. Fig. 3 shows associations between quintiles of WMH change and individual NPI score, MMSE and functional score trajectories between time-points.

3.5. Specific neuropsychiatric symptoms and longitudinal WMH volume change

We additionally performed an exploratory analysis to determine whether the most prevalent individual neuropsychiatric symptoms of apathy, irritability, depression and agitation were associated with WMH progression, adjusting for age, atrophy, MMSE and disability scores (Fig. A3, Supplementary Material). These individual neuropsychiatric symptoms were not associated with WMH progression, although there

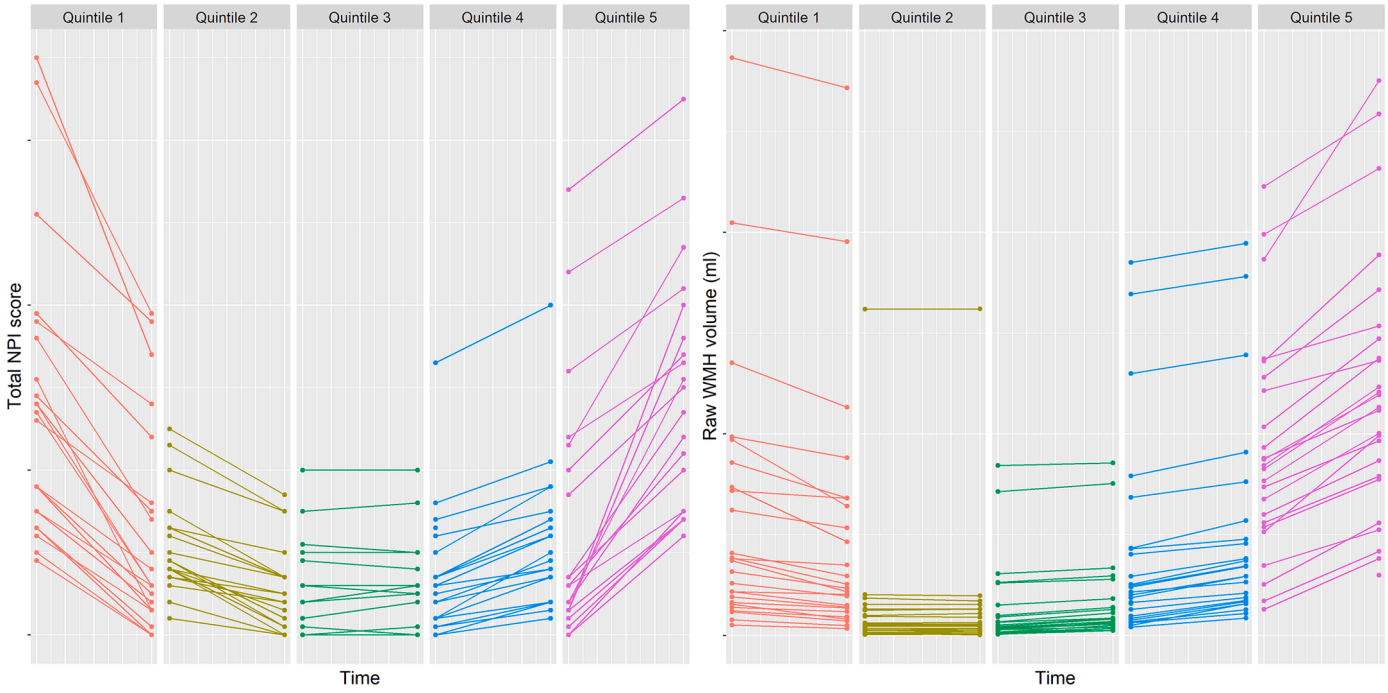

Fig. 1. (a) Individual participants' changes in white matter hyperintensity (WMH) volumes between baseline and follow-up by quintile of WMH volume change (b) Individual participants' changes in neuropsychiatric inventory (NPI) scores between baseline and follow-up by quintile of NPI score change Note: (a) Each line represents the WMH trajectory of an individual participant. Q1 = greatest reduction; Q5 = greatest increase; (b) Each line represents the NPI trajectory of an individual participant. Q1 = greatest reduction; Q5 = greatest increase.

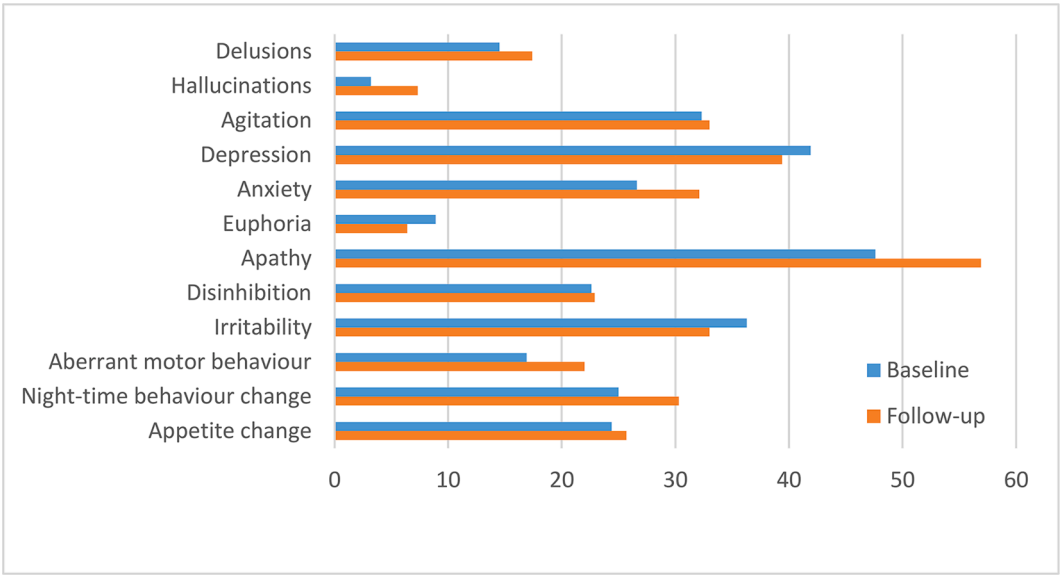

Fig. 2. Neuropsychiatric symptom prevalence (%) at baseline and follow-up.

was a trend towards an association with apathy (est 0.004, 95% CI: -0.0008 to 0.0088, $P = 0.09$) and irritability (est 0.01, 95% CI: 0 to 0.01, $P = 0.05$).

4. Discussion

We demonstrated that worsening neuropsychiatric symptoms were independently associated with WMH presence and intra-individual WMH progression in a cognitively impaired population, while WMH volumes remained stable in those with static neuropsychiatric symptoms. Moreover, WMH progression was more strongly associated with worsening neuropsychiatric symptoms than with a decline in either functional ability or MMSE scores over the same duration. Although our findings establish temporal associations rather than causality, this longitudinal analysis advances our knowledge of the natural clinical history of SVD in cognitive impairment.

Clinical symptoms and signs play a key role in detecting diseases. Our findings highlight how worsening neuropsychiatric symptoms, which can be readily reported to a doctor by a patient or their relative, may have potential as a subtle clinical marker of SVD progression over and above more overt clinical features such as decline in cognition or function.

Table 2
(a) Cross-sectional linear regression with baseline normalized WMH volume as the dependent variable; (b) Longitudinal linear mixed effects model: association of normalised longitudinal white matter hyperintensity (WMH) volumes with longitudinal total neuropsychiatric inventory (NPI) scores, $n = 116$*.

(a)	Baseline	(b)	Longitudinal				
Predictors	estimate	std error	statistic	*p*	estimate	95% CI	*p*
(Intercept)	1.221	0.45	2.68	0.007	1.2758	-0.0156 to 2.5672	0.053
BPF	-1.99	0.47	-4.21	<0.001	-2.0769	-3.434 to -0.719	0.003
Total NPI	0.004	0.001	2.75	0.006	0.0015	0.0003 to 0.0028	0.017
Vascular RFs	0.039	0.01	2.04	0.041	0.0421	-0.0112 to 0.0954	0.121
Age	0.013	0.002	5.55	<0.001	0.0135	0.0068 to 0.0202	<0.001
Interscan interval	-	-	-	-	0.0022	0.0016 to 0.0029	<0.001

(a) Note: estimates are based on normalized WMH as the dependent variable [cube root of (WMH volume cm^3 expressed as % ICV)]. Multiple R-squared: 0.3339 Adjusted R-squared: 0.3223. F-statistic: 28.58 on 4 and 228 DF. *P* value: < 2.2e-16.
(b) Note: Random effects σ2 = 0, τ00 Subject ID = 0.09. ICC = 0.97, n=116 Observations =221. Marginal/Conditional R2=0.31/0.97 *Analysis omitted 8 individuals without VRF data but see sensitivity analysis in Supplementary Appendix. Vascular risk factors = composite score of hypertension, hypercholesterolemia, diabetes smoking status. Baseline-only variables: age atrophy vascular risk factors. Longitudinal variables: WMH volumes. total NPI scores interscan interval.
Abbreviations: NPI = Neuropsychiatric inventory BPF = Brain Parenchymal Fraction RFs = risk factors.

4.1. Strengths and limitations

Our analysis of a cognitively impaired population takes a clinically practical approach, taking into account declining function and cognition over follow-up, both key features of the dementia phenotype. We analyzed continuous measures of exposure and outcome using linear mixed-effects models, a robust method accounting for intra-individual variation in WMH trajectory height. Our study participants represented a 'real-world' patient population since all participants initially presented to the memory clinic with cognitive complaints and all received diagnoses of cognitive impairment or dementia: we did not separate our analysis by cognitive impairment subtype, stratifying instead according to burden of cerebrovascular disease. The median 15-month interscan interval is shorter than that seen in previous longitudinal imaging studies assessing cognition and SVD [34], demonstrating that assessment of outcomes in similar populations at shorter intervals is clinically applicable, helping inform future study designs.

We did not make full use of the DAD subscores [35] but the total DAD score assesses both basic and instrumental activities of daily living and has been shown to detect clinically relevant differences [36] that other ADL scales do not. We used the MMSE to assess cognition. The MMSE has a relatively narrow scope for detecting mild cognitive impairment. However, it was widely used when the study first commenced in 1995, was undertaken by the majority of participants attending two imaging time-points, and we wanted to maximize the use of available cognitive data. The longitudinal nature of our analysis required selection of a sample that had MRI at two time-points, potentially reducing generalisability. Incomplete assessments are a well-documented inevitability of dementia research. To mitigate this limitation, we assessed differences between participants in the current analysis vs. those that were excluded, i.e. without follow-up MRI (see Table A2, Supplementary Material). We found only minor differences in cognitive test scores, age (but not after adjustment for confounders), and no differences in functional status. Although the absolute change in WMH volumes between visits was small, those with the highest baseline WMH volumes had the greatest WMH volume increase, consistent with previous findings in a stroke population [31]. Given relatively low levels of WMH burden and change, we may have underestimated the strength of association between longitudinal WMH volumes and NPI scores. Although there was a trend towards WMH volume change associations with irritability and apathy in our exploratory analysis, verification of these specific associations requires a larger sample size. The sample size used for this analysis was relatively small although this is not uncommon for longitudinal imaging studies in cognitively impaired populations [37]. Although we only assessed a single imaging marker of SVD (i.e. WMH), our analysis was based on the same MRI scanner using the same robust quantification method [38], thus limiting both acquisition-related and quantification method-related sources of variability [39]. However, given the numerous imaging markers of SVD, this analysis should be repeated in a larger sample incorporating multiple SVD features.

Previous work on longitudinal WMH associations with the NPI found that the presence (vs absence) of WMH progression was associated with increasing total NPI in a population without dementia at baseline [40]. Our analysis confirms and builds on these results, using continuous WMH volumes at both time-points, a more precise assessment of change, and additionally adjusts for vascular risk factors, head-size, and global brain atrophy. Our analysis predominantly assessed individuals with dementia in whom the NPI is validated [23], extending findings to a population with more dynamic brain and behavioral changes, at high risk for WMH progression and worsening neuropsychiatric symptoms. This is reflected by higher total NPI scores in our population, which is consistent with the known higher prevalence of neuropsychiatric symptoms in individuals with established dementia compared with mild cognitive impairment [7]. A detailed study of NPI subsyndromes and WMH found that hyperactivity, psychosis, affective symptoms, and apathy (rather than total NPI score) were associated with WMH volume change [41] and further work is needed to disentangle individual symptom associations. The present analysis adds clinical value to previous work by assessing the relative contributions of longitudinal change in functional and cognitive test scores. Other studies have assessed baseline WMH in relation to longitudinal NPI scores [42,43], with mixed findings (Suppl Table 1).

Our findings uncover the potential to monitor neuropsychiatric symptoms as a novel, easily identifiable, acceptable, and inexpensive clinical marker of WMH progression in cognitively impaired individuals, which can be readily tracked by caregivers outside of healthcare settings.

4.2. Implications and future research targets

These findings should incentivize researchers and clinicians to take worsening neuropsychiatric symptoms seriously in high-risk groups. These symptoms do not meet diagnostic criteria for stroke or dementia when considered in isolation but their clinical importance is increasingly apparent. This study provides motivation to crystallize the other features of the 'small vessel disease phenotype' across healthy older, stroke and cognitively impaired populations, using longitudinal clinicoradiological studies. Clinically identifying individuals who have the highest risk of SVD progression, at the earliest stages of disease, should be a priority for emerging SVD treatment trials.

Apathy was the most prevalent symptom in this population and is highly prevalent in dementia and stroke populations. Future longitudinal work is required to determine precisely whether apathy may manifest subclinically in the early stages of cognitive impairment, in individuals who have high stroke risk, or in individuals with so-called 'silent' SVD on brain imaging. Apathy is thought to arise from

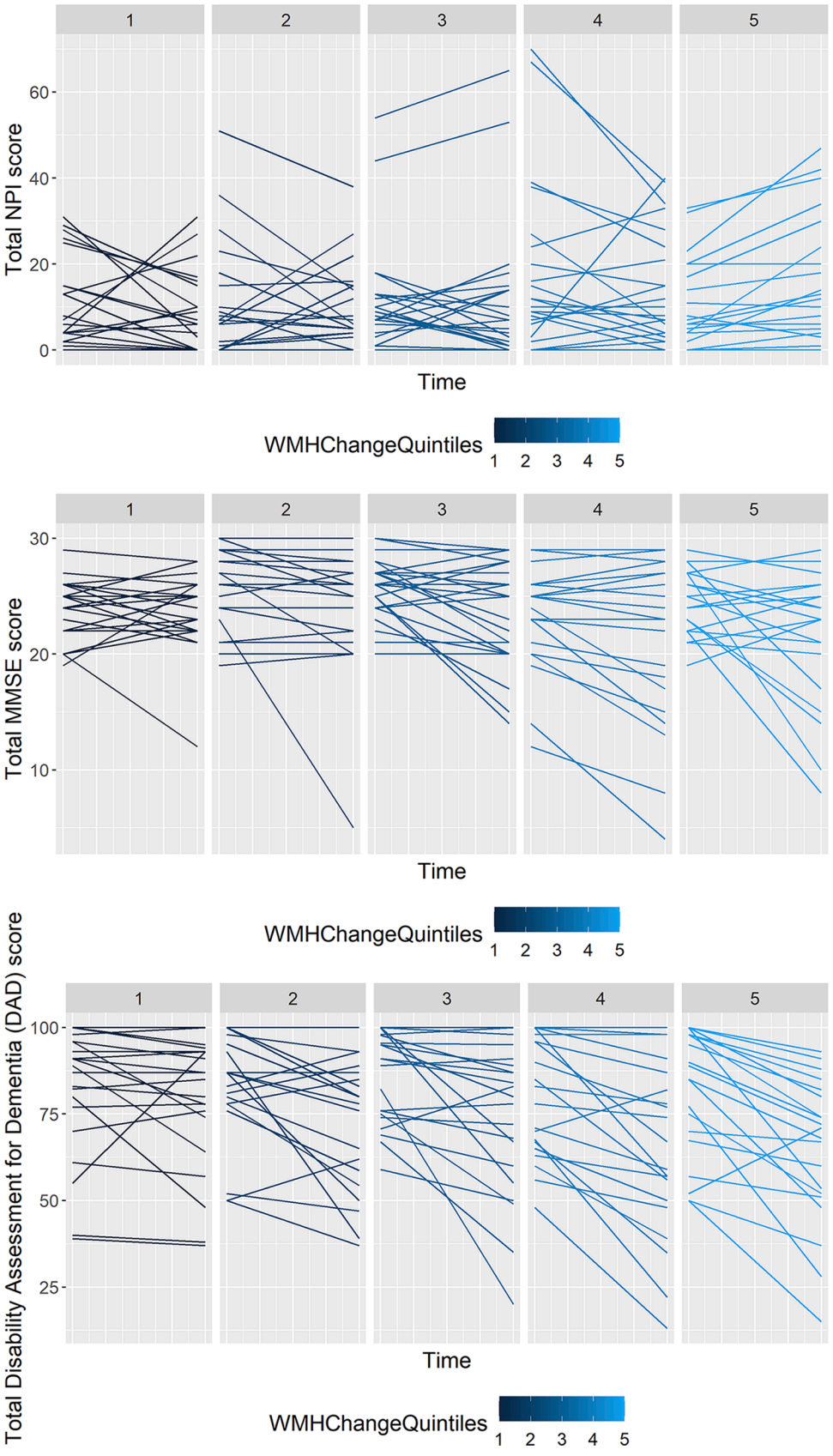

Fig. 3. Individual participants' changes in clinical scores (Neuropsychiatric Inventory [NPI], MMSE, disability) between baseline and follow-up by quintile of white matter hyperintensity (WMH) volume change. Note: Each line represents an individual participant's (a) NPI (b) MMSE (c) disability score from baseline to follow-up. Q1 (dark blue) = greatest WMH reduction; Q5 (light blue) = greatest WMH increase. These plots display WMH volume change by quintiles for display purposes only: all analyses presented used continuous longitudinal WMH volumes.

Table 3
(a) Cross-sectional linear regression with baseline normalized white matter hyperintensity (WMH) volume as a dependent variable: total neuropsychiatric inventory (NPI), MMSE, and Disability scores; (b) Longitudinal linear mixed effects model of longitudinal WMH volumes with longitudinal clinical scores: total NPI, MMSE, and Disability scores, $n = 124$.

(a) Linear regression					*(b) Linear mixed effects model*		
Predictors	*Estimates*	*std error*	*statistic*	*p*	*Estimates*	*95%CI*	*p*
(Intercept)	1.2433	0.464	2.67	0.0079	1.0493	-0.1692 to 2.2678	0.091
BPF	-2.117	0.535	-3.95	0.0001	-1.7309	-3.0145 to -0.4474	0.008
Total NPI	0.0052	0.001	3.11	0.0021	0.0016	0.0003 to 0.0029	0.015
MMSE	-0.001	0.006	-0.21	0.8313	-0.0004	-0.0047 to 0.0038	0.848
Disability (DAD)	0.0010	0.001	0.91	0.3626	-0.0005	-0.0016 to 0.0006	0.360
Age	0.0141	0.002	5.877134	<0.001	0.0145	0.0081 to 0.0210	<0.001
Interscan interval	-	-	-	-	0.0019	0.0010 to 0.0027	<0.001

(a) Note Multiple R-squared: 0.3224 Adjusted R-squared: 0.3074 F-statistic: 21.51 on 5 and 226 DF $p< 2.2e\text{-}16$.
(b) Note: Random effects $\sigma 2 = 0$ $\tau 00$ Subject ID = 0.09 ICC = 0.96 n=124 Observations =232 Marginal/Conditional R2=0.29/0.97 Baseline-only variables: age atrophy. Longitudinal variables: WMH volumes total NPI scores MMSE DAD interscan interval.
Abbreviations: BPF = Brain Parenchymal Fraction NPI = Neuropsychiatric Inventory MMSE = mini-mental state examination DAD = Disability Assessment for Dementia.

impaired connectivity in the pre-frontal cortico-subcortical and basal ganglia regions [44] and it is biologically plausible that SVD lesions could cause apathy due to direct structural damage in these regions. Although apathy can be a depressive symptom, it may be regarded as a syndrome in its own right [45]. Therefore, a more granular analysis of the apathy syndrome, and more detailed apathy measurement scales that distinguish apathy from depression and other neuropsychiatric symptoms is required.

This analysis also adds to the increasing number of studies documenting WMH reduction and demonstrates that WMH reduction and unchanging WMH are associated with fewer NPI symptoms.

Whether neuropsychiatric symptoms predate WMH, develop during a subclinical phase of WMH evolution or exclusively accompany established WMH is yet to be determined. The sequence of events needs to be clarified by identifying whether neuropsychiatric symptoms associate more strongly with acute, subacute, or chronic small vessel damage. Further research using serial MRI and shorter interscan intervals is required to assess whether these findings apply to individuals with dynamic lesion changes regardless of presentation, including imaging sequences which are sensitive to acute subcortical 'ischemia', tissue fluid, and changes in other structural SVD markers, e.g. Diffusion- and Susceptibility-Weighted Imaging. This will also help to clarify whether neuropsychiatric symptom severity and trajectory varies according to rate of WMH change, lesion location, and pre-existing small and large vessel disease. We need to identify which specific subsymptoms contribute to high and fluctuating total NPI scores in relation to WMH progression, powered by large sample sizes.

Future work should include Alzheimer's disease biomarkers and attempt to disentangle whether neuropsychiatric symptoms are exclusively attributable to a single pathology or whether, for example, a synergistic double-hit of small vessel dysfunction and β-amyloid accumulation plays a role.

We should also extend findings to populations with higher SVD burden, including vascular populations that commonly experience neuropsychiatric symptoms, e.g. individuals with mild stroke, additionally investigating relationships with post-stroke cognitive impairment.

5. Conclusions

SVD is associated with a wide spectrum of clinical features in older people, including cognitive, stroke, gait, and other neuropsychiatric manifestations. Worsening neuropsychiatric symptoms may usefully contribute to a multimodal approach to identify those at highest risk of WMH progression, which itself is associated with worse outcomes including declining cognition and increasing stroke risk. Identifying early, easily identifiable clinical markers of worsening SVD is important, not only for prognostication and developing vascular risk prevention strategies but also because identifying the natural history of SVD earlier in its clinical course will allow us to test future treatments as early as possible before cognitive impairment and stroke develop and progress.

CRediT authorship contribution statement

Una Clancy: Formal analysis, Writing – original draft, Writing – review & editing. **Joel Ramirez:** Project administration, Formal analysis, Writing – original draft, Writing – review & editing. **Francesca M. Chappell:** Formal analysis, Supervision, Writing – original draft, Writing – review & editing. **Fergus N. Doubal:** Formal analysis, Writing – original draft, Writing – review & editing. **Joanna M. Wardlaw:** Formal analysis, Writing – original draft, Writing – review & editing. **Sandra E. Black:** Conceptualization, Funding acquisition, Project administration, Data curation, Supervision, Formal analysis, Writing – original draft, Writing – review & editing.

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Supplementary materials

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