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Neuropsychiatric symptoms and white matter hyperintensities in older adults without dementia

Ioannis Liampas,[1] Vasileios Siokas,[1] Elli Zoupa,[2] Panayiota Kyriakoulopoulou,[3] Polyxeni Stamati,[1] Antonios Provatas,[1] Zisis Tsouris,[1] Vana Tsimourtou,[1] Constantine G. Lyketsos,[4] and Efthimios Dardiotis[1,4]

[1]*Department of Neurology, University Hospital of Larissa, School of Medicine, University of Thessaly, Larissa, Greece*
[2]*Larisa Day Care Center of People with Alzheimer's Disease, Association for Regional Development and Mental Health (EPAPSY), Marousi, Greece*
[3]*School of Medicine, University of Patras, Rio Patras, Greece*
[4]*Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD, USA*

ABSTRACT

Objective: We aimed to examine associations between neuropsychiatric symptoms (NPS) and white matter hyperintensities (WMH) status in older adults without dementia under the hypothesis that WMH increased the odds of having NPS.

Design: Longitudinal analysis of data acquired from the National Alzheimer's Coordinating Center Uniform Data Set.

Settings: Data were derived from 46 National Institute on Aging – funded Alzheimer's Disease Research Centers.

Participants: NACC participants aged ≥ 50 years with available data on WMH severity with a diagnosis of mild cognitive impairment (MCI) or who were cognitively unimpaired (CU) were studied. Among 4617 CU participants, 376 had moderate and 54 extensive WMH. Among 3170 participants with MCI, 471 had moderate and 88 had extensive WMH.

Measurements: Using Cardiovascular Health Study (CHS) scores, WMH were coded as no to mild (CHS score: 0–4), moderate (score: 5–6) or extensive (score: 7–8). NPS were quantified on the Neuropsychiatric Inventory Questionnaire. Binary logistic regression models estimated the odds of reporting each of 12 NPS by WMH status separately for individuals with MCI or who were CU.

Results: Compared to CU individuals with no to mild WMH, the odds of having elation [9.87, (2.63–37.10)], disinhibition [4.42, (1.28–15.32)], agitation [3.51, (1.29–9.54)] or anxiety [2.74, (1.28–5.88)] were higher for the extensive WMH group, whereas the odds of having disinhibition were higher for the moderate WMH group [1.94, (1.05–3.61)]. In the MCI group, he odds of NPS did not vary by WMH status.

Conclusions: Extensive WMH were associated with higher odds of NPS in CU older adults but not in those with MCI.

Key words: elation, disinhibition, agitation, anxiety

Introduction

White matter hyperintensities (WMH) are a very common magnetic resonance imaging (MRI) finding in older individuals, appearing with increased signal on T2-weighted and fluid-attenuated inversion recovery sequences. While they are most often regarded as a feature of small vessel disease, multiple pathophysiological mechanisms have been incriminated such as blood-brain barrier leakage, neuroinflammation and neurodegeneration (Fernando *et al.*, 2006; Shim *et al.*, 2015). Demyelination, axonal loss and gliosis with variable pathological severity are also among the nonspecific neuropathological substrates of WMH (Gouw *et al.*, 2011). WMH prevalence increases with age and vascular risk burden (Ryu *et al.*, 2014). WMH have

Correspondence should be addressed to: Ioannis Liampas, Department of Neurology, University Hospital of Larissa, Faculty of Medicine, University of Thessaly, Mezourlo Hill, Larissa, Greece. Email: iliampas@uth.gr, liampasioannes@gmail.com. Received 17 Feb 2024; revision requested 17 Feb 2024; revised version received 26 Mar 2024; accepted 15 Apr 2024. First published online 19 April 2024.

been related to cognitive decline, incident stroke and dementia, as well as fatigue, physical (e.g., imbalance, gait abnormalities), and neuropsychiatric symptoms (NPS) (Clancy *et al.*, 2021; Debette and Markus, 2010).

NPS (such as depression, anxiety, delusions, and apathy) are non-cognitive disturbances that are quite prevalent in individuals with MCI and almost universal in those with dementia (Lyketsos *et al.*, 2011, 2002). Among cognitively unimpaired (CU) older adults, NPS have been linked to worse cognitive test performance (Liampas *et al.*, 2022b), more precipitous cognitive decline (Krell-Roesch *et al.*, 2021) and an elevated hazard of Alzheimer's (AD) or non-AD dementia (Liew, 2020). In individuals with MCI, NPS have been linked to steeper cognitive trajectories (Roberto *et al.*, 2021) and inflated risk of future dementia (Liew, 2019), while in those with dementia, NPS are a harbinger of more abrupt cognitive decline (Defrancesco *et al.*, 2020), among other unfavorable outcomes (Bränsvik *et al.*, 2021). Therefore, the presence of NPS in older adults should be regarded as a precursor of cognitive decline throughout the normal cognitive aging to dementia continuum.

Of note, in the continuum of healthy aging – dementia, Taragano and colleagues introduced the construct of mild behavioral impairment (MBI) – the neuropsychiatric equivalent of MCI –, as a transitional stage between normal aging and dementia which confers greater risk of incident dementia than MCI (Taragano *et al.*, 2009). Although an affinity towards non-AD dementias is apparent (frontotemporal dementia [FTD] and Lewy body dementia [LBD]), many individuals with MBI may convert to AD as well, owing to its considerably larger prevalence (Taragano *et al.*, 2018). The predominant hypothesis suggests that the association between NPS and cognitive decline probably reflects the relationship of NPS with undergoing neuropathological alterations (Peters and Lyketsos, 2015). Different NPS have been related to different neurodegenerative processes and by extension to heterogeneous cognitive trajectories and progression to different neurocognitive entities. For instance, psychosis has been linked to neuritic plaques, neurofibrillary tangles and Lewy body disease (an in turn, incident AD and Lewy body dementia [LBD]), agitation and aggression have been associated with TDP-43 pathology (a common substrate of FTD), whereas results on the involvement of vascular lesions in MBI have been inconsistent (Devanand *et al.*, 2022; Matsuoka *et al.*, 2023).

To date, few have investigated the relationship between WMH and NPS in individuals without dementia (MCI or normal cognition). These studies had several limitations such as small samples, not accounting for the confounding of neurocognitive status with vascular risk, non-distinctions between CU and MCI individuals, use of composite NPS scores over individual NPS (and then focus on depression and anxiety). It is not surprising that they have reported contradictory results (Chan *et al.*, 2022; Clancy *et al.*, 2021; Miao *et al.*, 2021; Misquitta *et al.*, 2020; Staekenborg *et al.*, 2008; Tumati *et al.*, 2023; Yang *et al.*, 2022). The aim in this was to estimate the associations between WMH and individual NPS in older adults without dementia. Specifically, we hypothesized that the odds of having NPS would be to the presence of WMH in both CU and MCI.

Methods and materials

This cross-sectional analysis capitalized on data from the ongoing Uniform Data Set (UDS). UDS is a central repository of multidisciplinary, longitudinally collected data by National Institute on Aging / National Institute of Health - funded Alzheimer's Disease Research Centers (ADRCs) across the United States (Beekly *et al.*, 2007; Morris *et al.*, 2006; Siokas *et al.*, 2022; Weintraub *et al.*, 2009). UDS was initiated in 2005 and since has been stewarded by the National Alzheimer's Coordinating Center (NACC). Clinician-, self- and family-referred volunteers, or actively recruited individuals with a cognitive status ranging from normal cognition to dementia are enrolled according to each ADRC's discrete protocol. Standardized evaluations take place on an approximately annual basis. Participants or surrogates provide informed consent before participation. All procedures are overseen by local Institutional Review Board(s) and performed in accordance with the ethical standards of the declaration of Helsinki and its later amendments. For further information on access to the NACC database, please contact NACC at https://naccdata.org/.

Eligibility criteria and diagnostic procedures

The current analysis was based on UDS data from the December 2022 data freeze, collected from a total of 46 ADRCs. Older (≥ 50 years) participants with available data on WMH (only the 1st visit with available data was considered for eligibility) and a concurrent diagnosis of MCI or CU, were eligible (those with dementia or cognitive impairment not MCI were excluded). Cognitive diagnoses were established by either expert consensus panels (in the majority of cases) or single physicians (i.e., those who conducted the examination), according to each

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ADRC's discrete protocol. CU was defined by the absence of a diagnosis of dementia, MCI or cognitive impairment not MCI. MCI [subjective and objective (based on the typical threshold of 1.5 standard deviations) cognitive disorder in the absence of repercussions on daily life] and dementia were diagnosed using standard clinical criteria (McKeith *et al.*, 2017; McKhann *et al.*, 1984; Neary *et al.*, 1998; Petersen *et al.*, 1999; Roman *et al.*, 1993; Winblad *et al.*, 2004). Participants with cognitive impairment who did not clearly fit into these categories were diagnosed with cognitive impairment – not MCI.

Measurement of NPS

The Neuropsychiatric Inventory Questionnaire (NPI-Q) is an informant administered, widely used tool for the evaluation of NPS in dementia research (Kaufer *et al.*, 2000; Liampas *et al.*, 2024). NPI-Q evaluates 12 domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, night-time behaviors, and eating behaviors. Informants initially report the presence or absence of cardinal symptomatology for each domain in the month preceding the examination and subsequently rate the severity of any symptoms according to a 3-point severity scale: mild (noticeable, but not a significant change); moderate (significant, but not a dramatic change); or severe (very marked or prominent; a dramatic change) (Liampas *et al.*, 2022c). For the purposes of the current analysis, participants were dichotomized for presence of each NPS (0: absent; 1: present). Delusions and hallucinations were grouped together (psychotic symptoms) owing to their very low prevalence. Two additional composite NPS indices were analyzed: total number of NPS (0–11) and total NPS severity score (0–22). For the latter, absence of NPS was scored with 0, mild symptomatology conferred 1 point and moderate to severe symptomatology conferred 2 points.

Measurement of WMH

The Cardiovascular Health Study (CHS) score is an ordinal quantification scale that uses visual inspection of a MRI to WMH burden ranging from 0 to 8 (Manolio *et al.*, 1994). Periventricular and subcortical volumes of WMH are assessed on spin density-weighted axial images and scored between 0 (no WMH) and 8 (extensive, confluent WMH). Areas of large vessel infarction or small vessel lacunar strokes are excluded from the scoring. In the NACC database, based on WMH status, participants are coded as follows: with no to mild WMH (CHS score: 0–4), with moderate WMH (CHS score: 5–6) and with extensive WMH (CHS score: 7–8).

Covariates considered

Chronological age upon entry to the study and years of formal education were treated as scale variables. Sex, race (Caucasian, African American, other) and the following comorbidities were treated as categorical (yes/no) variables: cerebrovascular disease (CEVD), atrial fibrillation (AF), hypertension, diabetes mellitus (DM) and dyslipidaemia. CEVD was defined as a positive history of stroke and/or transient ischemic attack. Comorbidities were primarily evaluated based on participant or co-participant reporting. However, to limit the amount of missing data, clinician reporting was utilized when necessary.

Regarding cognition, the five MCI subtypes in the NACC database were treated as dichotomous variables, i.e., MCI memory: yes/no; MCI language: yes/no; MCI executive function: yes/no; MCI visuospatial: yes/no; MCI attention: yes/no. On the other hand, Mini-Mental State Examination (MMSE) scores were treated as scale variables. Instead of MMSE, Montreal Cognitive Assessment (MoCA) was utilized in the last (3rd) version of UDS. To limit the amount of missing data, MoCA values were converted to MMSE scores according to conversion tables provided by a NACC crosswalk study (Liampas *et al.*, 2023; Monsell *et al.*, 2016).

Statistical analysis

Individuals with unimpaired cognition or with MCI were analyzed separately using the same approach. Demographic and other characteristics of the three groups defined by WMH status were compared using analysis of variance (ANOVA; scale variables) and Pearson's chi-squared test (categorical variables). The frequencies of different NPS subtypes were also compared between the three WMH groups using Pearson's chi-squared test.

The unadjusted and adjusted odds, and 95% confidence intervals, of having each NPS by WMH severity were estimated. Binary logistic regression models were performed to estimate the adjusted odds of reporting each NPS by WMH status. Models were adjusted for age, years of education, sex, race, history of CeVD, AF, hypertension, DM and dyslipidaemia. To account for cognitive status, analyses involving CU participants were additionally adjusted for MMSE scores, whereas analyses involving MCI participants were additionally adjusted for MCI subtypes. Finally, composite NPS measures (scale variables: total number of NPS or total NPS severity) were sequentially inserted into univariate generalized linear models

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Table 1. Baseline comparison of older, cognitively unimpaired individuals by white matter hyperintensities status

Variable	CHS score <5 ($N = 4187$)	CHS score: 5–6 ($N = 376$)	CHS score: 7–8 ($N = 54$)	*P*-value
Age in years	69.6 ± 8.7	74.8 ± 8.5	77.4 ± 7.9	**<0.001**
Formal education in years	16.3 ± 2.8	16.1 ± 2.8	16.7 ± 2.7	0.112
Mini-mental state-examination score	29.3 ± 1.2	29.0 ± 1.5	28.6 ± 2.3	**<0.001**
Sex (male/female %)	1502/2685 (93/90%)	102/274 (6/9%)	19/35 (1/1%)	**0.003**
Race (Caucasian / African American / other %)	3422/500/265 (92/85/92%)	274/83/19 (7/14/7%)	45/6/3 (1/1/1%)	**<0.001**
Cerebrovascular disease (No/Yes %)	4090/97 (91/79%)	357/19 (8/15%)	47/7 (1/6%)	**<0.001**
Atrial fibrillation (No/Yes %)	3975/198 (91/86%)	344/29 (8/12%)	47/4 (1/2%)	**0.024**
Diabetes mellitus (No/Yes %)	3686/239 (91/87%)	310/33 (8/12%)	43/4 (1/1%)	**0.031**
Hypertension (No/Yes %)	2473/1704 (94/86%)	146/228 (5/12%)	16/38 (1/2%)	**<0.001**
Dyslipidaemia (No/Yes %)	2051/2083 (93/89%)	141/228 (6/10%)	24/29 (1/1%)	**<0.001**
Average number of NPS per individual	0.74 ± 1.36	0.79 ± 1.44	1.35 ± 1.86	**0.017**
Average NPS severity per individual	0.97 ± 2.00	1.00 ± 1.97	1.85 ± 2.75	**0.021**
Psychotic symptoms (No/Yes %)	3814/31 (91/91%)	343/3 (8/9%)	41/0 (1/0%)	0.839
Depression (No/Yes %)	3242/592 (91/91%)	297/48 (8/7%)	31/10 (1/2%)	0.209
Anxiety (No/Yes %)	3306/527 (91/90%)	295/49 (8/8%)	29/11 (1/2%)	**0.043**
Agitation (No/Yes %)	3643/199 (91/90%)	329/17 (8/8%)	36/5 (1/2%)	0.128
Disinhibition (No/Yes %)	3738/100 (91/85%)	331/14 (8/12%)	38/3 (1/3%)	0.059
Irritability (No/Yes %)	3359/482 (91/91%)	303/42 (8/8%)	33/8 (1/1%)	0.397
Elation (No/Yes %)	3808/34 (91/90%)	345/1 (8/3%)	38/3 (1/8%)	**<0.001**
Apathy (No/Yes %)	3631/201 (91/90%)	326/20 (8/9%)	38/3 (1/1%)	0.774
Motor symptoms (No/Yes %)	3766/64 (91/92%)	340/5 (8/7%)	40/1 (1/1%)	0.883
Appetite disorders (No/Yes %)	3633/194 (91/88%)	320/23 (8/10%)	36/5 (1/2%)	0.059
Nighttime behaviors (No/Yes %)	3265/466 (91/89%)	289/46 (8/9%)	32/9 (1/2%)	0.162

Bold denotes statistically significant differences between the two groups; CHS, cardiovascular health study.

(GLMs) as dependent variables (robust to violations of normality). Again, both measures were separately analyzed in CU and MCI individuals. GLMs were adjusted for the same covariates as described before.

Statistical analyses were performed using the IBM SPSS Statistics Software Version 26 (Chicago, IL, USA). Despite performing multiple comparisons, the conventional threshold of $\alpha = 0.05$ was implemented for the revelation of statistical significance in order to retain a fair statistical power for our analyses, considering the low frequency of certain NPS, and the low prevalence of extensive WMH.

Results

Participant characteristics – CU group

In total, 4617 CU participants with available WMH assessments were eligible for the analysis. Of these 376 had moderate and 54 had extensive WMH. Baseline differences by WMH status are in Table 1. The sample comprised predominantly older, well-educated, Caucasian individuals. CU individuals with greater WMH burden were older, more often of female sex and African American, and performed worse on MMSE. Vascular comorbidities were more common in the presence of more severe WMH. Participants with normal cognition and extensive WMH had greater average severity of NPS. Anxiety and elation were the only NPS that were more prevalent in the high severity WMH group.

Associations between WMH status and NPS – CU group

After adjusting for age, education, MMSE scores, sex, race and vascular risk factors, the average number of NPS was 1.28 (95% CI: 1.08–1.48) for those with no to mild WMH, 1.38 (1.13–1.63) for those with moderate and 1.99 (1.50–2.49) for those with severe. *Post hoc* comparisons (pooled $p = 0.007$) found that the total number of NPS was greater in CU individuals with extensive WMH compared to those with no to mild WMH [Mean difference (MD) = 0.71 (0.24–1.18), $p = 0.003$] or compared to those with moderate WMH [MD = 0.61 (0.12–1.10), $p = 0.014$]. Average NPS severity by WMH status was 1.71 (1.41–2.00) for those with no to mild WMH, 1.83 (1.46–2.19) for those with moderate and 2.76 (2.03–3.49) for those with severe. *Post hoc* comparisons (pooled $p = 0.008$) revealed that total

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Table 2. Odds of having neuropsychiatric symptoms by white matter hyperintensities (WMH) status among older, cognitively unimpaired adults. The group with the lowest cardiovascular health study (CHS) score (<5) was used as reference

Variable	Pooled *P*-value	CHS score: 5–6 OR (95%CI)	*P*-value	CHS score: 7–8 OR (95%CI)	*P*-value
Adjusted analyses					
Psychotic symptoms	$p = 1.000$	0.95 (0.27–3.34)	0.936	NA	0.998
Depression	$p = 0.144$	0.93 (0.65–1.33)	0.694	2.14 (0.98–4.70)	0.057
Anxiety	$\mathbf{p = 0.034}$	1.07 (0.75–1.53)	0.707	**2.74 (1.28–5.88)**	**0.010**
Agitation	$\mathbf{p = 0.049}$	1.06 (0.60–1.86)	0.843	**3.51 (1.29–9.54)**	**0.014**
Disinhibition	$\mathbf{p = 0.011}$	**1.94 (1.05–3.61)**	**0.035**	**4.42 (1.28–15.32)**	**0.019**
Irritability	$p = 0.540$	1.01 (0.69–1.49)	0.963	1.68 (0.67–4.18)	0.267
Elation	$\mathbf{p = 0.002}$	0.34 (0.05–2.93)	0.360	**9.87 (2.63–37.10)**	**<0.001**
Apathy	$p = 0.608$	0.96 (0.54–1.68)	0.873	1.85 (0.54–6.38)	0.330
Motor symptoms	$p = 0.814$	0.89 (0.31–2.56)	0.830	1.86 (0.24–14.53)	0.554
Appetite disorders	$p = 0.164$	1.32 (0.81–2.16)	0.266	2.44 (0.83–7.15)	0.105
Nighttime behaviors	$p = 0.162$	1.27 (0.88–1.81)	0.198	1.91 (0.81–4.49)	0.137
Unadjusted analyses					
Psychotic symptoms	$p = 0.839$	1.08 (0.33–3.54)	$p = 0.904$	NA	0.564
Depression	$p = 0.209$	0.89 (0.64–1.22)	$p = 0.450$	1.77 (0.86–3.62)	0.116
Anxiety	$\mathbf{p = 0.043}$	1.04 (0.76–1.43)	$p = 0.799$	**2.38 (1.18–4.79)**	**0.012**
Agitation	$p = 0.128$	0.95 (0.57–1.57)	$p = 0.830$	2.54 (0.99–6.55)	0.061
Disinhibition	$p = 0.059$	1.58 (0.89–2.80)	$p = 0.112$	2.95 (0.90–9.72)	0.062
Irritability	$p = 0.397$	0.97 (0.69–1.35)	$p = 0.840$	1.69 (0.78–3.68)	0.182
Elation	$\mathbf{p < 0.001}$	0.33 (0.04–2.38)	$p = 0.243$	**8.84 (2.60–30.04)**	**<0.001**
Apathy	$p = 0.774$	1.11 (0.69–1.78)	$p = 0.670$	1.43 (0.44–4.66)	0.555
Motor symptoms	$p = 0.883$	0.87 (0.35–2.17)	$p = 0.757$	1.47 (0.20–10.87)	0.703
Appetite disorders	$p = 0.059$	1.35 (0.86–2.11)	$p = 0.191$	2.60 (1.01–6.70)	0.040
Nighttime behaviors	$p = 0.162$	1.12 (0.81–1.55)	$p = 0.512$	1.97 (0.94–4.15)	0.069

Bold denotes statistically significant differences between the two groups; between group differences were considered significant only if among group differences were significant as well – *p*-value for among group differences in provided by each NPS; analyses were adjusted for age, education, MMSE scores, sex, race, and vascular risk factors; OR, odds ratio; CI, confidence interval; NA, non-applicable – no participant with extensive WMH had psychotic symptoms.

NPS severity was greater in the group of CU individuals with extensive WMH compared to those with no to mild WMH [MD = 1.05 (0.37–1.74), $p = 0.003$], and compared to those with moderate WMH [MD = 0.93 (0.21–1.65), $p = 0.011$].

The odds of having each NPS by WMH status in CU individuals are in Table 2. The odds of elation (~9.9 times), disinhibition (~4.4 times), agitation (~3.5 times) and anxiety (~2.7 times) were significantly elevated in CU older adults with extensive WMH compared to those with no or mild WMH (Figure 1). On the other hand, compared to those with no or mild WMH,moderate WMH increased only the odds of having disinhibition by about 1.9 times. Of note, the older adults with extensive WMH had higher odds (between 1.7 and 2.1 times) of having every remaining NPS, apart from psychotic symptoms, but findings were not significant.

Participant characteristics – MCI group

In total, 3170 participants with MCI had available WMH assessments and were eligible for the analysis. Among them, 471 had moderate and 88 had extensive WMH. Baseline differences by WMH status are in Table 3. The MCI group primarily consisted of older, well-educated, Caucasian individuals. Older adults with MCI and greater WMH burden were older, more often African American and performed worse on MMSE. Vascular comorbidities were more prevalent in the presence of more severe WMH. The number of total NPS, total NPS severity, as well as the presence of individual NPS did not differ by extent of WMH changes.

Associations between WMH status and NPS – MCI group

After adjusting for age, education, MCI subtypes, sex, race and vascular risk factors, the average total number of NPS was 2.32 (2.03–2.61) for those with no to mild, 2.50 (2.17–2.83) for those with moderate and 1.89 (1.34–2.45) for those with severe WMH. Post hoc comparisons showed that the total number of NPS did not differ between groups. Average NPS severity was 3.14 (2.69–3.59) for those with no to

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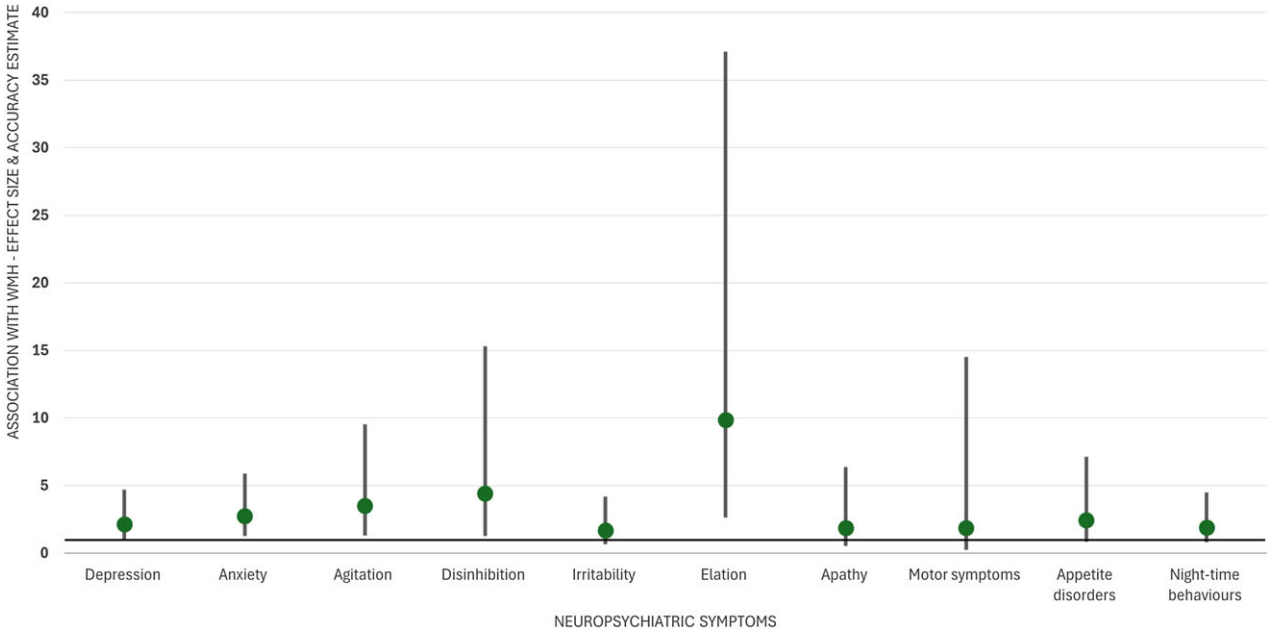

Figure 1. Associations between extensive white matter hyperintensities and neuropsychiatric symptoms in cognitively unimpaired older adults. Odds ratios and 95% confidence intervals (95% CIs) are provided.

mild, 3.41 (2.90–3.92) for those with moderate and 2.56 (1.71–3.41) for those with severe WMH. Post hoc comparisons found no NPS differences by WMH group. The odds of having each NPS by WMH status in older adults with MCI are in Table 4. Those with moderate WMH had approximately 34% more odds of having anxiety. However, considering the small effect size and inconsistency (no other significant associations were found between WMH and NPS in the MCI group – an opposite trend was revealed) this finding is likely the result of chance.

Discussion

We report that CU older adults with extensive WMH in MRI studies had higher odds of having NPS compared to individuals with no to mild WMH, in particular, elation, disinhibition, agitation, and anxiety. In the CU group with moderate WMH only disinhibition was associated with WMH in comparison with the reference group (no to mild WMH). Our estimates accounted for important demographic and vascular-related factors, as well as cognitive testing. These findings align with the hypothesis that severe WMH contribute to the overall neuropsychiatric burden of CU individuals, independent of cognitive impairment or vascular risk burden. Moderate WMH do not appear to appreciably increase NPS risk overall in this group.

Older individuals with MCI and extensive or moderate WMH did not have greater odds of NPS compared to those with no to mild WMH. This lack of association may stem from the fact that co-existing neuropathologic alterations in older adults with MCI are almost universal: AD pathology predominates with vascular and Lewy body (LB) pathologies not infrequent (Dugger *et al.*, 2015; Schneider *et al.*, 2009). Therefore, those with no to mild (as well as moderate) WMH may have more co-existing neurodegenerative alterations that account for cognitive impairment. Considering the well-established, strong relationships between amyloid or LB pathology and several NPS it is likely that any association of WMH with NPS was overwhelmed by that of the other pathologies (Gibson *et al.*, 2023; Goukasian *et al.*, 2019; Krell-Roesch *et al.*, 2019). These findings may provide a potential explanation for the incongruous results of previous publications that did not consistently reveal a relationship between WMH and NPS in individuals without dementia: analyzing individuals without dementia, especially small groups, with and without MCI, with MCI owing to heterogeneous neuropathologies or with different levels of MCI and NPS severity may modulate true associations between WMH and NPS.

WMH have been associated with disrupted brain network dynamics (Tuladhar *et al.*, 2015). Impaired transferring of information between interconnected cerebral areas is theorized to underlie the relationship between WMH and cognitive impairment (Yang *et al.*, 2020). The same mechanism could be crucial in the occurrence of neuropsychiatric symptoms in individuals with WMH (Desmarais

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Table 3. Baseline comparison of older individuals with mild cognitive impairment (MCI) by white matter hyperintensities status

Variable	CHS score <5 ($N = 2611$)	CHS score: 5–6 ($N = 471$)	CHS score: 7–8 ($N = 88$)	*P*-value
Age in years	71.8 ± 8.8	76.9 ± 7.2	78.8 ± 7.3	**<0.001**
Formal education in years	16.1 ± 3.1	16.0 ± 3.0	15.5 ± 3.4	0.283
Mini-mental state-examination score	27.4 ± 2.6	27.1 ± 2.5	26.8 ± 2.5	**0.012**
Sex (male/female %)	1355/1256 (83/81%)	226/245 (14/16%)	48/40 (3/3%)	0.246
Race (Caucasian / African American / other %)	2240/240/131 (83/73/82%)	374/74/23 (14/22/15%)	68/15/5 (3/5/3%)	**<0.001**
Cerebrovascular disease(No/Yes %)	2486/125 (84/62%)	415/56 (14/27%)	66/22 (2/11%)	**<0.001**
Atrial fibrillation (No/Yes %)	2423/177 (83/73%)	416/54 (14/22%)	75/11 (3/5%)	**<0.001**
Diabetes mellitus (No/Yes %)	2250/234 (83/76%)	380/62 (14/20%)	67/11 (3/4%)	**0.007**
Hypertension (No/Yes %)	1362/1238 (88/77%)	161/310 (10/19%)	23/65 (2/4%)	**<0.001**
Dyslipidaemia (No/Yes %)	1156/1431 (86/80%)	155/309 (12/17%)	26/62 (2/3%)	**<0.001**
Average number of NPS per individual	2.10 ± 2.14	2.07 ± 2.09	1.61 ± 1.99	0.136
Average NPS severity per individual	2.84 ± 3.31	2.80 ± 3.21	2.15 ± 3.18	0.203
Psychotic symptoms (No/Yes %)	2337/129 (82/83%)	421/23 (15/15%)	78/3 (3/2%)	0.830
Depression (No/Yes %)	1602/856 (82/84%)	300/141 (15/14%)	60/21 (3/2%)	0.145
Anxiety (No/Yes %)	1654/806 (82/83%)	294/149 (15/15%)	62/19 (3/2%)	0.190
Agitation (No/Yes %)	2041/423 (82/84%)	369/74 (15/14%)	73/8 (3/2%)	0.225
Disinhibition (No/Yes %)	2172/291 (83/81%)	382/61 (14/17%)	72/9 (3/2%)	0.490
Irritability (No/Yes %)	1668/797 (83/82%)	293/150 (14/15%)	57/24 (3/3%)	0.701
Elation (No/Yes %)	2400/66 (82/84%)	430/13 (15/16%)	81/0 (3/0%)	0.308
Apathy (No/Yes %)	1912/554 (82/84%)	352/91 (15/14%)	67/14 (3/2%)	0.386
Motor symptoms (No/Yes %)	2273/194 (82/83%)	408/34 (15/15%)	76/5 (3/2%)	0.852
Appetite disorders (No/Yes %)	2045/414 (82/84%)	374/69 (15/14%)	70/11 (3/2%)	0.617
Nighttime behaviors (No/Yes %)	1762/658 (82/84%)	323/112 (15/14%)	62/14 (3/2%)	0.207

Bold denotes statistically significant differences between the two groups; CHS, cardiovascular health study.

et al., 2021). The functional connectivity of the brain is compromised across multiple psychiatric conditions with younger ages of onset (e.g., autism, attention deficit hyperactivity disorder, bipolar disorder, schizophrenia, and so on) and may be similarly undermined in older adults with late-onset NPS. Therefore, the correlation of greater WMH load with reduced functional connectivity may provide a potential explanation for the prominent associations between extensive WMH and NPS (Crockett *et al.*, 2021; Quandt *et al.*, 2020). Future research conducting mediation analyses could explore whether disrupted brain connectivity assumes a pivotal role in NPS among older individuals, whether different mechanisms are implicated or whether WMH are just epiphenomena of neurodegeneration with variable severity across the spectrum of heterogeneous neuropathologies.

Of note, WMH may not only contribute directly to the epidemiology of NPS but also via their interference with cognition. WMH burden has been correlated with global but also domain-specific cognitive impairment (Prins and Scheltens, 2015). More specifically, frontal operations such as executive function and attention appear to be correlated to the volume of periventricular and subcortical WMH (Puzo *et al.*, 2019; Sudo *et al.*, 2012). Again, disrupted brain (mainly fronto-parietal) networks seem to mediate these cognitive associations (Li *et al.*, 2015). Of interest, specific cognitive deficits have been more strongly linked to particular NPS: impairments in principally frontally mediated functions have been specifically associated with anxiety and lability symptoms such as disinhibition, agitation, irritability and elation (Liampas *et al.*, 2022b; Rosenberg *et al.*, 2011). Of course, some spatial specificity is to be expected; WMH in strategic brain regions may be more or less related to different cognitive and NPS manifestations (Brugulat-Serrat *et al.*, 2020; Lampe *et al.*, 2019). Based on the above, our findings may at least partially be driven by the cognitive associations of WMH.

Overall, our findings enhance current knowledge on the associations between neurodegenerative alterations and NPS in older adults without dementia. Previous positron emission tomography

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Table 4. Odds of having neuropsychiatric symptoms by white matter hyperintensities(WMH) status among older adults with mild cognitive impairment (MCI). The group with the lowest cardiovascular health study (CHS) score (<5) was used as reference

Variable	Pooled *P*-value	CHS score: 5–6 OR (95%CI)	*P*-value	CHS score: 7–8 OR (95%CI)	*P*-value
Adjusted analyses					
Psychotic symptoms	$p = 0.552$	1.15 (0.70–1.89)	0.573	0.52 (0.12–2.21)	0.379
Depression	$p = 0.643$	1.05 (0.83–1.34)	0.668	0.80 (0.46–1.39)	0.430
Anxiety	$\mathbf{p = 0.032}$	**1.34 (1.05–1.69)**	**0.017**	0.78 (0.44–1.40)	0.405
Agitation	$p = 0.147$	1.03 (0.76–1.38)	0.870	0.43 (0.18–1.01)	0.054
Disinhibition	$p = 0.068$	1.47 (1.05–2.04)	0.024	1.35 (0.65–2.81)	0.425
Irritability	$p = 0.164$	1.25 (0.98–1.58)	0.068	0.91 (0.53–1.56)	0.728
Elation	$p = 0.486$	1.49 (0.78–2.84)	0.230	NA	0.997
Apathy	$p = 0.721$	1.00 (0.76–1.32)	0.990	0.77 (0.40–1.47)	0.420
Motor symptoms	$p = 0.574$	1.12 (0.73–1.72)	0.602	0.59 (0.18–1.94)	0.386
Appetite disorders	$p = 0.794$	0.98 (0.72–1.34)	0.894	0.78 (0.38–1.61)	0.499
Nighttime behaviors	$p = 0.140$	1.01 (0.78–1.30)	0.951	0.51 (0.26–1.00)	0.049
Unadjusted analyses					
Psychotic symptoms	$p = 0.830$	0.99 (0.63–1.56)	0.965	0.70 (0.22–2.24)	0.542
Depression	$p = 0.145$	0.88 (0.71–1.09)	0.246	0.66 (0.40–1.08)	0.097
Anxiety	$p = 0.190$	1.04 (0.84–1.29)	0.720	0.63 (0.37–1.06)	0.078
Agitation	$p = 0.225$	0.97 (0.74–1.27)	0.812	0.53 (0.25–1.11)	0.085
Disinhibition	$p = 0.490$	1.19 (0.89–1.60)	0.246	0.93 (0.46–1.87)	0.847
Irritability	$p = 0.701$	1.07 (0.87–1.33)	0.528	0.88 (0.54–1.43)	0.609
Elation	$p = 0.308$	1.10 (0.60–2.01)	0.758	NA	0.136
Apathy	$p = 0.386$	0.89 (0.70–1.15)	0.369	0.72 (0.40–1.29)	0.270
Motor symptoms	$p = 0.852$	0.98 (0.67–1.43)	0.902	0.77 (0.31–1.93)	0.577
Appetite disorders	$p = 0.617$	0.91 (0.69–1.20)	0.512	0.78 (0.41–1.48)	0.440
Nighttime behaviors	$p = 0.207$	0.93 (0.74–1.17)	0.532	0.61 (0.34–1.09)	0.090

Bold denotes statistically significant differences between the two groups; between group differences were considered significant only if among group differences were significant as well – *p*-value for among group differences in provided by each NPS; analyses were adjusted for age, education, MCI subtypes, sex, race and vascular risk factors; OR, odds ratio; CI, confidence interval; NA, non-applicable – no participant with extensive WMH had elation.

(PET) imaging studies of individuals without dementia has indicated that higher Aβ42 deposition is related to higher NPI-Q scores (Ng *et al.*, 2021). Apathy, anxiety, depression and psychotic symptoms were most consistently associated with amyloid pathology – while agitation, disinhibition or elation present weaker to marginal associations (Gibson *et al.*, 2023; Goukasian *et al.*, 2019; Krell-Roesch *et al.*, 2019; Ng *et al.*, 2021). On the other hand, elation and disinhibition appear to be linked to the presence of frontotemporal lobar degeneration, whereas psychotic symptoms and impulse control disorders are very prevalent with LB and PD neuropathology, respectively (Cajanus *et al.*, 2019; Cotta Ramusino *et al.*, 2021; Sokołowski *et al.*, 2023). Although significant overlap is to be expected, based on the neuropsychiatric manifestations of an individual -especially as part of a comprehensive examination- clinicians and researcher can make some inferences about potential ongoing neurodegenerative alterations and select more sophisticated laboratory means to establish more accurate diagnoses.

Strengths and limitations

Our study has several strengths including the large sample of individuals with available WMH assessments with an adequate number of individuals with extensive WMH. The NPI-Q was uniformly used to assess the presence of NPS. The neurocognitive status of the participants (along with important demographic and vascular-related confounders) was accounted for in the analytical part of the article.

This analysis has several weaknesses, as well. First, the number of certain NPS (especially psychotic and motor symptoms and secondarily apathy) was very small, underpowering several aspects of our analysis. Therefore, it is not surprising that we failed to reproduce some previously established associations, such as between WMH and apathy (Manca *et al.*, 2022). This is reflected in the broad confidence intervals and may have obscured several non-trivial associations. Second, although several crucial factors and covariates were taken into account, our findings may have been driven by residual confounding (it is not be possible

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to capture the effect of every potential confounder) or the non-trivial proportion of missing data (Liampas *et al.*, 2022a; Samara *et al.*, 2022). Third, the presence or absence of WMH was not uniformly assessed by a central, blinded evaluator (or group of evaluators). Some variability is expected among different assessors in the quantification of WMH. In addition, we did not correct our findings for multiple comparisons to retain a fair statistical power despite the low frequency of certain NPS and the low prevalence of extensive WMH. Nevertheless, in view of the sizeable and consistent associations in the CU group we are confident that our results reflect true associations. Moreover, we did not include additional imaging (or not) biomarkers, such as global or parietal atrophy, hippocampal volumes, and so on. Finally, another limitation is the observational nature of our study. Hence, it is not possible to make etiologic inferences about NPS and WMH.

Conclusions

Extensive WMH were associated with the overall neuropsychiatric burden of CU individuals, independent of cognitive impairment or vascular risk burden. The odds of elation, disinhibition, agitation and anxiety were particularly elevated. On the other hand, WMH were not related to the neuropsychiatric burden of individuals with MCI. Considering that alternative neuropathologic alterations in older adults with MCI (especially AD, vascular and LB pathology) may account for cognitive impairment (instead of extensive WMH), the very strong established relationships between these pathologies and NPS is likely overwhelming the association of WMH with NPS. Therefore, it would be interesting if future research looked into the same associations using larger samples of individuals with different MCI subtypes and by extension different underlying pathologies.

Data availability and materials

For further information on access to the NACC database, please contact NACC (contact details can be found at https://naccdata.org/).

Conflict of interest

The authors declare that they have no conflict of interest.

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Description of author(s)' roles

IL: original draft preparation, data curation, formal analysis, design of the study, interpretation of data, and review & editing of manuscript; VS, EZ, PS: validation, review & editing of manuscript; AP, ZT, VT: data curation review & editing of manuscript; CGL, ED: conceptualization, formulation of research question, design of the study, supervision, review & editing.

Ethical standards

Participants or surrogates provide informed consent before participation. All procedures are overseen by Institutional Review Boards at each ADRC. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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