Journal of the International Neuropsychological Society (2023), **29**, 431–438
doi:10.1017/S1355617722000480

Research Article

Neuropsychiatric symptoms are associated with exacerbated cognitive impairment in covert cerebral small vessel disease

Anne Arola[1,2], Tuuli Levänen[1], Hanna M. Laakso[1,2], Johanna Pitkänen[3], Juha Koikkalainen[4,5], Jyrki Lötjönen[4,6], Antti Korvenoja[7], Timo Erkinjuntti[3], Susanna Melkas[3] and Hanna Jokinen[1,2]

[1]HUS Neurocenter, Division of Neuropsychology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland, [2]Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, Helsinki, Finland, [3]Department of Neurology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland, [4]Combinostics Ltd, Tampere, Finland, [5]Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland, [6]Department of Neuroscience and Biomedical Engineering, School of Science, Aalto University, Espoo, Finland and [7]HUS Diagnostic Center, Radiology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

Abstract

Objectives: Neuropsychiatric symptoms are related to disease progression and cognitive decline over time in cerebral small vessel disease (SVD) but their significance is poorly understood in covert SVD. We investigated neuropsychiatric symptoms and their relationships between cognitive and functional abilities in subjects with varying degrees of white matter hyperintensities (WMH), but without clinical diagnosis of stroke, dementia or significant disability. **Methods:** The Helsinki Small Vessel Disease Study consisted of 152 subjects, who underwent brain magnetic resonance imaging (MRI) and comprehensive neuropsychological evaluation of global cognition, processing speed, executive functions, and memory. Neuropsychiatric symptoms were evaluated with the Neuropsychiatric Inventory Questionnaire (NPI-Q, $n = 134$) and functional abilities with the Amsterdam Instrumental Activities of Daily Living questionnaire (A-IADL, $n = 132$), both filled in by a close informant. **Results:** NPI-Q total score correlated significantly with WMH volume ($r_s = 0.20$, $p = 0.019$) and inversely with A-IADL score ($r_s = -0.41$, $p < 0.001$). In total, 38% of the subjects had one or more informant-evaluated neuropsychiatric symptom. Linear regressions adjusted for age, sex, and education revealed no direct associations between neuropsychiatric symptoms and cognitive performance. However, there were significant synergistic interactions between neuropsychiatric symptoms and WMH volume on cognitive outcomes. Neuropsychiatric symptoms were also associated with A-IADL score irrespective of WMH volume. **Conclusions:** Neuropsychiatric symptoms are associated with an accelerated relationship between WMH and cognitive impairment. Furthermore, the presence of neuropsychiatric symptoms is related to worse functional abilities. Neuropsychiatric symptoms should be routinely assessed in covert SVD as they are related to worse cognitive and functional outcomes.

Keywords: Neuropsychiatric symptoms; Cerebral small vessel disease; White matter hyperintensities; Cognition; Cognitive impairment; Instrumental activities of daily living

(Received 1 February 2022; final revision 18 May 2022; accepted 19 May 2022; First Published online 30 August 2022)

Introduction

Neuropsychiatric symptoms are highly prevalent in cognitive decline and dementia (Geda et al., 2008; Steinberg et al., 2008). Since neuropsychiatric symptoms are associated with higher risk of institutionalisation and even death, they are an extremely important factor to consider in clinical settings (Okura et al., 2011).

Both cognitive decline and neuropsychiatric symptoms occur in cerebral small vessel disease (SVD). The consistent associations between SVD brain pathology (white matter hyperintensities [WMH], lacunes, cerebral microbleeds, and brain atrophy) and cognitive impairment have been established in previous studies (for a recent review see Hamilton et al., 2021). More severe WMH have been linked to apathy, fatigue and delirium as well as overall severity of neuropsychiatric symptoms (Clancy et al., 2021; Kim et al., 2013). Apathy has been found to relate to SVD both in terms of disrupted white matter track connectivity and worse cognitive functioning (Lohner et al., 2017; Tay et al., 2019). Overall SVD-related brain changes have been shown to relate to depression, and an association between white matter tract damage and depression has been found in patients with symptomatic SVD including stroke (Brookes et al., 2014; Rensma et al., 2018). WMH have also been shown to predict cognitive decline and an increase in depressive symptoms over time in Alzheimer's disease (Puzo et al., 2019).

Previous research has shown that neuropsychiatric symptoms are associated with cognitive impairment. In community-dwelling subjects, cognitive impairment was related to higher incidence of neuropsychiatric symptoms and specific cognitive domains were

Corresponding author: Anne Arola, Email: anne.arola@helsinki.fi

Cite this article: Arola A., Levänen T., Laakso H.M., Pitkänen J., Koikkalainen J., Lötjönen J., Korvenoja A., Erkinjuntti T., Melkas S., & Jokinen H. (2023) Neuropsychiatric symptoms are associated with exacerbated cognitive impairment in covert cerebral small vessel disease. *Journal of the International Neuropsychological Society*, **29**: 431–438, https://doi.org/10.1017/S1355617722000480

associated with specific neuropsychiatric symptoms (executive functions and visuomotor speed with hyperactivity and affective symptoms; language and visual memory with psychosis symptoms, Xu et al., 2015). In overt SVD with dementia, higher prevalence of neuropsychiatric symptoms has been found to relate to worse cognitive outcomes (Chin et al., 2012).

In a memory clinic sample of elderly subjects, who were free from dementia at baseline, increased WMH over time was associated with more neuropsychiatric symptoms, and an increase in both WMH and neuropsychiatric symptoms was related to cognitive decline over a 2-year period (Kan et al., 2020). Pathological brain changes such as WMH and lacunes have been associated with higher incidence of neuropsychiatric symptoms in patients with subcortical vascular impairment (Kim et al., 2013). In particular, WMH were found to relate to higher incidence of apathy and higher overall frequency of neuropsychiatric symptoms.

The majority of the previous research has focused on symptomatic SVD. The combined effects of WMH and neuropsychiatric symptoms on cognitive and functional abilities are not known in the preclinical stages of SVD, where brain changes are detectible but no criteria are met for clinical diagnosis of stroke, dementia or significant disability (covert SVD).

We examined neuropsychiatric symptoms and domain-specific cognitive performance in subjects with varying degrees of WMH who were free from dementia and stroke and were independent in their basic activities of daily living. Specifically, we investigated whether (a) WMH are associated with neuropsychiatric symptoms, (b) neuropsychiatric symptoms are related to cognitive performance and instrumental activities of daily living (IADL), and (c) neuropsychiatric symptoms moderate the relationship between WMH and cognitive and functional outcomes.

Method

Subjects and design

The Helsinki Small Vessel Disease Study is a cohort study investigating covert cerebral SVD through brain imaging, clinical, and cognitive characteristics in older individuals. The study protocol has been described in detail previously (Arola et al., 2021; Jokinen et al., 2022). Briefly, the study included subjects who had recently undergone a brain scanning due to transient ischemic attack (26%), dizziness (18%), headache/migraine (10%), subjective cognitive complaints (4%), visual symptoms (11%), fall (7%), syncope (3%), or other reasons (20%). The subjects were recruited from the imaging registry of the Helsinki University Hospital in Finland between October 2016 and March 2020. A total of 152 subjects with varying degrees of WMH took part in the study including comprehensive neurological and neuropsychological assessments, self- and informant-filled questionnaires and a brain magnetic resonance imaging (MRI) with standard protocol carried out at three visits within approximately 1 month.

The inclusion criteria were: (a) age 65–75 years at the time of enrollment; (b) place of residence within the Helsinki and Uusimaa hospital district; (c) occurrence of not more than minor, temporary, and local neurological symptoms (having manifested 3 to 12 months before the enrollment), or no neurological symptoms at all; (d) functional independence in daily activities as defined by a modified Rankin Scale score (van Swieten, Koudstaal, Visser, Schouten, & van Gijn, 1988) of 0–2; and (e) fluent Finnish language skills. The main exclusion criteria included significant neurological diseases, severe psychiatric disorders and factors that might hinder the administration of the neuropsychological tests (such as sight or hearing disabilities) or that might affect undergoing the MRI. Additional exclusion criteria based on MRI findings were defined as follows: (a) cortical infarct; (b) subcortical infarct larger than 15 mm (20 mm on diffusion-weighted images); (c) hemorrhage larger than microbleed (over 10 mm); (d) brain tumor; and (e) contusion, traumatic subarachnoid or intracranial hemorrhage, distinct diffuse axonal injury.

The current study included 134 subjects who had available evaluations of neuropsychiatric symptoms (see details below).

Ethics approval

The study was approved by the Ethics Committee of the Helsinki University Hospital and conducted according to the Declaration of Helsinki. Informed written consent was received from each subject.

Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Magnetic resonance imaging

A 3T MRI scanner with 32-channel head coil was used for the imaging. The protocol consisted of fast three plane localizer, 3D FLAIR SPACE, 3D T2 SPACE, 3D T1 MPRAGE, 3D gradient echo susceptibility weighted imaging sequence, 3D gradient echo sequence with magnetization transfer pulse on and off.

WMH of presumed vascular origin were defined on FLAIR sequences as hyperintense areas in the white matter without cavitation (Wardlaw et al., 2013). A board certified neuroradiologist first evaluated WMH visually using the modified Fazekas scale (Pantoni et al., 2004); 0 = none, 1 = mild, 2 = moderate, and 3 = severe, accounting for deep and subcortical WMH. Total WMH and gray matter (GM) volumes as well as periventricular and deep WMH volumes were segmented on FLAIR images with an automated multistage segmentation method based on the Expectation-Maximization algorithm (Wang et al., 2012). Three step method described earlier was used for the segmentation (Koikkalainen et al., 2016). Intracranial volume was used to normalize the total WMH and GM volume (ml) and the non-normality of the distribution was accounted for using a logarithmic transformation.

Evaluation of cognitive functioning

Cognitive functioning was evaluated using a comprehensive neuropsychological assessment comprised of both paper-and-pencil and computerised tests described in detail previously (Jokinen et al., 2022). Briefly, the following domains were evaluated; processing speed, executive functions, working memory, memory and learning, visuospatial perception, and verbal reasoning (see Supplemental Table 1 for specific cognitive tests). Domain scores were constructed as follows: (1) the distributions of the raw scores were checked for outliers and non-normality, and square root or logarithmic transformations were applied where appropriate, (2) variables were standardized into z scores based on the data of the present sample, (3) the scales were inverted, when needed, so that higher values represented better performance in all variables, (4) composite measures were calculated by taking the mean of the standardized test scores within each domain. A global cognition score consisted of a standardized mean score comprised of the six domain scores. In this study, we focused on global cognitive

https://doi.org/10.1017/S1355617722000480 Published online by Cambridge University Press

score as the primary measure of cognitive performance. In addition, we examined three specific cognitive domains, namely, processing speed, executive functions and memory, as the core domains most susceptible in the covert stages of SVD (Du et al., 2020; Knopman et al., 2015; Prins et al., 2005). Additionally, we used Montreal Cognitive Assessment (MoCA) for descriptive purposes to indicate the level of general cognitive status of the subjects (Nasreddine et al., 2005).

Evaluation of neuropsychiatric symptoms

Neuropsychiatric symptoms were reported by a close informant using the Neuropsychiatric Inventory Questionnaire (NPI-Q, Cummings et al., 1994). NPI-Q includes items on 12 neuropsychiatric symptoms (delusions, hallucinations, aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, motor disturbance, night time disruptive behaviors, and appetite). For each symptom, the first question is whether the subject has had the symptom (yes or no) in the last month. We did not include the sentence "Please answer the following questions based on changes that have occurred since the patient first began to experience memory problems" from the original instruction, since not all of our subjects had experienced memory problems. NPI-Q total score is the sum of the occurrence of the 12 symptoms. The severity of the NPI-Q ranges between 1 and 3 (1 = mild, 2 = moderate, and 3 = severe) for each neuropsychiatric symptom. A total of 134 informants filled in the NPI-Q.

Evaluation of functional abilities

Instrumental activities of daily living were used as a measure of functional abilities. They were assessed with the short version of the Amsterdam Instrumental Activities of Daily Living (A-IADL) questionnaire also filled in by a subject's close informant (Jutten et al., 2017). The short version includes 30 questions assessing complex activities on areas such as taking care of household chores, work or finances, using appliances or a computer, as well as leisure activities. Scoring ranges from 0 (no difficulty) to 4 (unable to do activity) based on how performance is currently compared to the past performance. Item response theory is used to get a total score and higher scores show better functioning. A total of 132 informants filled in the A-IADL.

Statistical analyses

First, we used Spearman's correlations to examine the bivariate associations between NPI-Q total score and sex, age, and years of educations as well as the MRI volumetrics (total, periventricular, deep WMH and GM volumes). Second, we ran a logistic regressions with the MRI volumetrics as the independent variables and the neuropsychiatric symptoms (present/absent) as the dependent variable. Third, we ran linear regression analyses with the neuropsychiatric symptoms (present/absent) as the independent variable and the cognitive or functional outcomes as the dependent variable (five analyses: global cognition, processing speed, executive functioning, memory and A-IADL). Fourth, we repeated the linear regression analyses by adding in the interaction terms (neuropsychiatric symptoms [present/absent] x WMH), as the independent variables and cognitive composite scores as well as A-IADL as the dependent variables. We then repeated the third and fourth steps for the most common neuropsychiatric symptoms (depression, irritability, night time disruptive behaviours, apathy, and changes in appetite) as the independent variables. All analyses were controlled for sex, age, and education (years). The false discovery rate (FDR) correction was used for multiple analysis accounting for the five dependent variables in each set of analyses.

Table 1. Characteristics for 134 subjects with NPI-Q data

	Subjects
Demographics	
Age, mean (SD)	70.7 (2.9)
Sex, female/male, *n*	81/53
Education, years, mean (SD)	12.8 (4.5)
WMH	
Fazekas score, none, mild, moderate, severe, *n*	12/68/37/17
WMH volume, ml, mean (SD)	9.9 (12.4)
Clinical characteristics	
Hypertension, *n* (%)	91 (68.4)
Diabetes, *n* (%)	30 (22.4)
Hypercholesterolemia, *n* (%)	104 (77.6)
A-IADL, mean (SD)	66.7 (4.7)
MoCA score, mean (SD)	23.5 (3.3)

A-IADL = Amsterdam Instrumental Activities of Daily Living questionnaire; MoCA = Montreal Cognitive Assessment; WMH = white matter hyperintensities.

Results

Subject characteristics

The present study sample consisted of 134 subjects with informant-filled NPI-Q, who did not differ from those with missing data ($n = 18$) in sex, age, education, WMH volume, A-IADL or MoCA scores (all p-values > 0.05). Exact number of subjects also varied depending on the NPI-Q item, most had 18 missing values, but night time disruptive behaviors had 21 missing values (usually due to the informant being unsure how to answer that particular question). Demographic and clinical information can be found in Table 1. A-IADL score ranged between 43.6 and 70.0. Descriptives of the cognitive, A-IADL and NPI-Q scores in groups based on WMH severity (Fazekas score none/mild vs. moderate/severe) are presented in Supplemental Table 2. Of the subjects, 62% had no neuropsychiatric symptoms, 16% had one symptom and 22% had two or more symptoms. The most common neuropsychiatric symptoms in our sample were depression (25%), irritability (21%), night time disruptive behaviors (15%), apathy (11%) and changes in appetite (11%). The occurrence of each neuropsychiatric symptom of the NPI-Q are detailed in Figure 1. The distribution of the NPI-Q severity score was as follows: 0, $n = 85$ (63%); 1, $n = 21$ (16%); 2, $n = 12$ (9%); 3, $n = 6$ (5%); 4, $n = 6$ (5%), 8, $n = 2$ (2%), 9, $n = 1$ (1%), and 13, $n = 1$ (1%).

Relationships between NPI-Q and MRI volumetrics

NPI-Q total score correlated significantly with total WMH volume ($r_s = 0.20$, $p = 0.019$), and more specifically with periventricular WMH volume ($r_s = 0.20$, $p = 0.024$) and deep WMH volume ($r_s = 0.19$, $p = 0.028$), but it was not related to total GM volume ($r_s = 0.04$), age, sex or years of education (all $p > 0.05$). Total WMH volume was significantly associated with the presence of neuropsychiatric symptoms (binary variable) also after adjusting for age, sex, and education (OR 2.89, CI 95% 1.13–7.43, $p = 0.027$).

Relationships between NPI-Q, cognitive scores and A-IADL

NPI-Q total score did not have significant bivariate correlations with cognitive composite scores (r_s values between −0.08 and −0.13, all p-values > 0.05). After adjusting for sex, age, and education (years), there were no statistically significant associations

https://doi.org/10.1017/S1355617722000480 Published online by Cambridge University Press

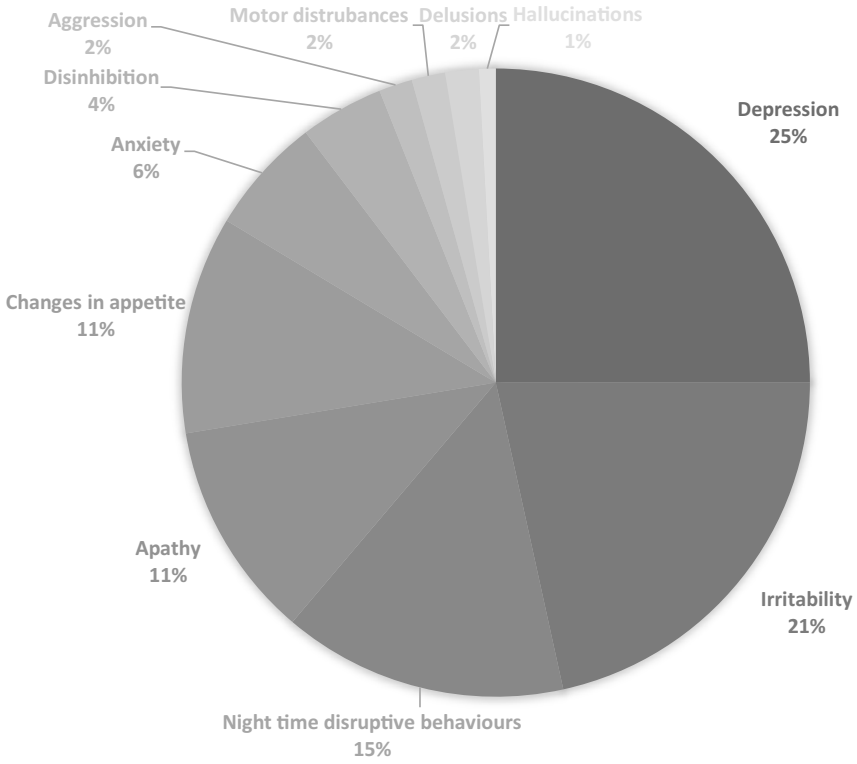

Figure 1. Occurrence of different neuropsychiatric symptoms (in percentages) based on the Neuropsychiatric Inventory Questionnaire (NPI-Q) from most common to least common clockwise.

between the presence of neuropsychiatric symptoms and cognitive functioning (standardized ß between −0.06 and −0.13, all *p*-values > 0.05). However, there were significant synergistic interactions between the presence of neuropsychiatric symptoms and WMH volume on all cognitive composite scores (Figure 2). Subjects with presence of any neuropsychiatric symptom together with higher levels of WMH volume had disproportionately low cognitive abilities. The synergistic interaction between the presence of neuropsychiatric symptoms and WMH volume on A-IADL was not significant (standardized ß −0.18, $p > 0.05$).

NPI-Q total score correlated inversely with A-IADL score ($r_s = -0.41$, $p < 0.001$). After adjusting for sex, age, and education, there was a significant association between the presence of neuropsychiatric symptoms and A-IADL (standardized ß −0.37, $p < 0.001$). The interaction between the presence of neuropsychiatric symptoms and WMH volume on A-IADL was not significant (*p*-value > 0.05).

Associations between most common NPI-Q symptoms, cognitive scores and A-IADL

The presence of depression was significantly associated with global cognition (standardized ß −0.19, $p < 0.014$, $f^2 = 0.05$) and A-IADL (standardized ß −0.43, $p < 0.001$, $f^2 = 0.21$), but not with specific cognitive domains (standardized ß between −0.11 and −0.14, all *p*-values > 0.05). There were significant interactions between the presence of depression and WMH volume on all the cognitive composite scores and A-IADL (Figures 3 and 4). Presence of depression together with higher levels of WMH volume associated with disproportionately poor cognitive composite and A-IADL scores. Irrespective of WMH, the presence of apathy was significantly associated with global cognition (standardized ß −0.29, $p < 0.001$, $f^2 = 0.06$), processing speed (standardized ß −0.23, $p = 0.005$, $f^2 = 0.05$), executive functions (standardized ß −0.19, $p = 0.017$, $f^2 = 0.03$), and memory (standardized ß −0.22, $p = 0.005$, $f^2 = 0.04$) as well as A-IADL (standardized ß −0.46, $p < 0.001$, $f^2 = 0.25$). The interactions between the presence of apathy, WMH and all the outcome variables were not significant (standardized ß between −0.07 and −0.19, all *p*-values > 0.05). The associations between the other most common neuropsychiatric symptoms (irritability, night time disruptive behaviors and changes in appetite) and cognitive and functional outcomes were statistically nonsignificant (all *p*-values > 0.05 after FDR correction).

Discussion

We assessed the occurrence of neuropsychiatric symptoms and their relationship with MRI volumetrics and cognitive and functional abilities in covert SVD. The most common neuropsychiatric symptoms in our sample were depressive symptoms, irritability, night time disruptive behaviors, apathy, and changes in appetite. Neuropsychiatric symptoms had significant correlations with total WMH volume, and with deep and periventricular WMH volume, but not with total GM volume. Neuropsychiatric symptoms were not directly related to cognitive functioning. Instead, the presence of neuropsychiatric symptoms together with higher total WMH volume was associated with exacerbated cognitive impairment in all the cognitive composite scores (global cognition, processing speed, executive functions, and memory). Furthermore, neuropsychiatric symptoms were related to worse functional abilities.

Depressive symptoms were the most common symptoms in our sample. Depressive symptoms together with higher levels of WMH volumes were related to worse cognitive and functional abilities. Apathy symptoms were related to worse cognitive and functional

https://doi.org/10.1017/S1355617722000480 Published online by Cambridge University Press

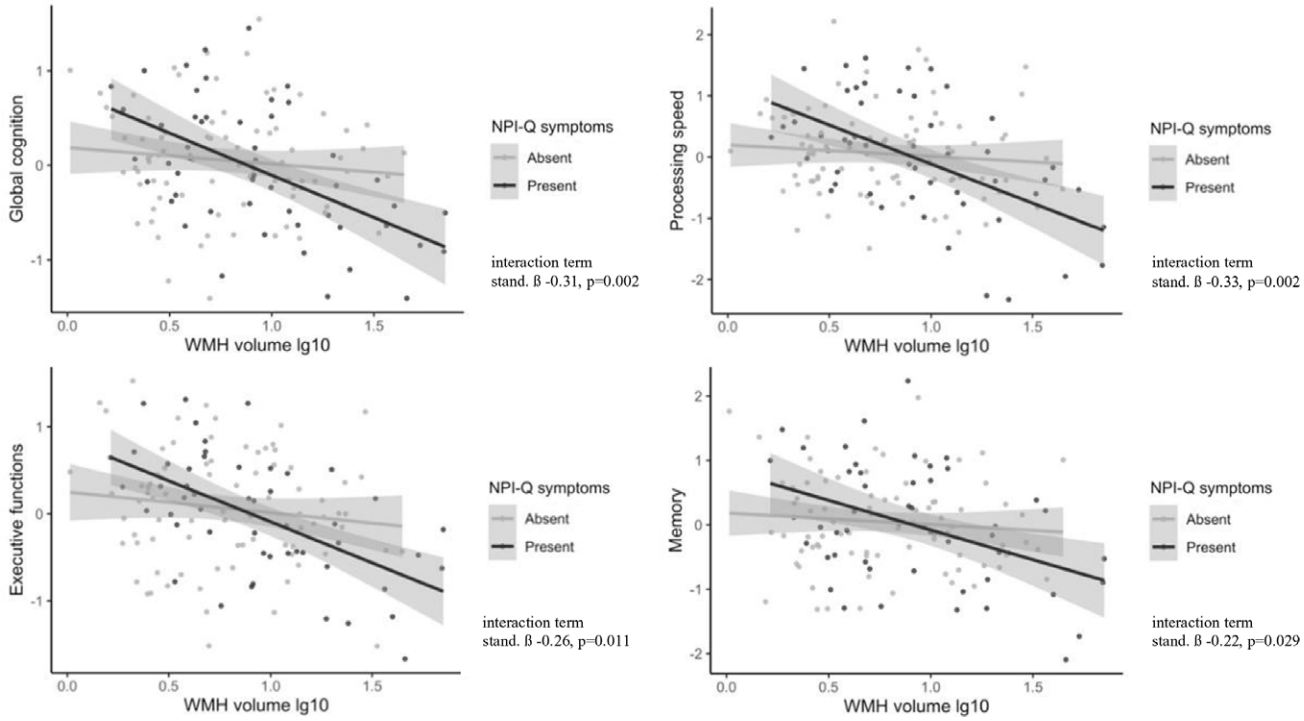

Figure 2. Interactions between white matter hyperintensities volume, presence or absence of informant-evaluated neuropsychiatric symptoms based on the Neuropsychiatric Inventory Questionnaire (NPI-Q) and cognitive functioning. Gray areas represent 95% confidence intervals. All interactions were significant also after False Discovery Rate corrections.

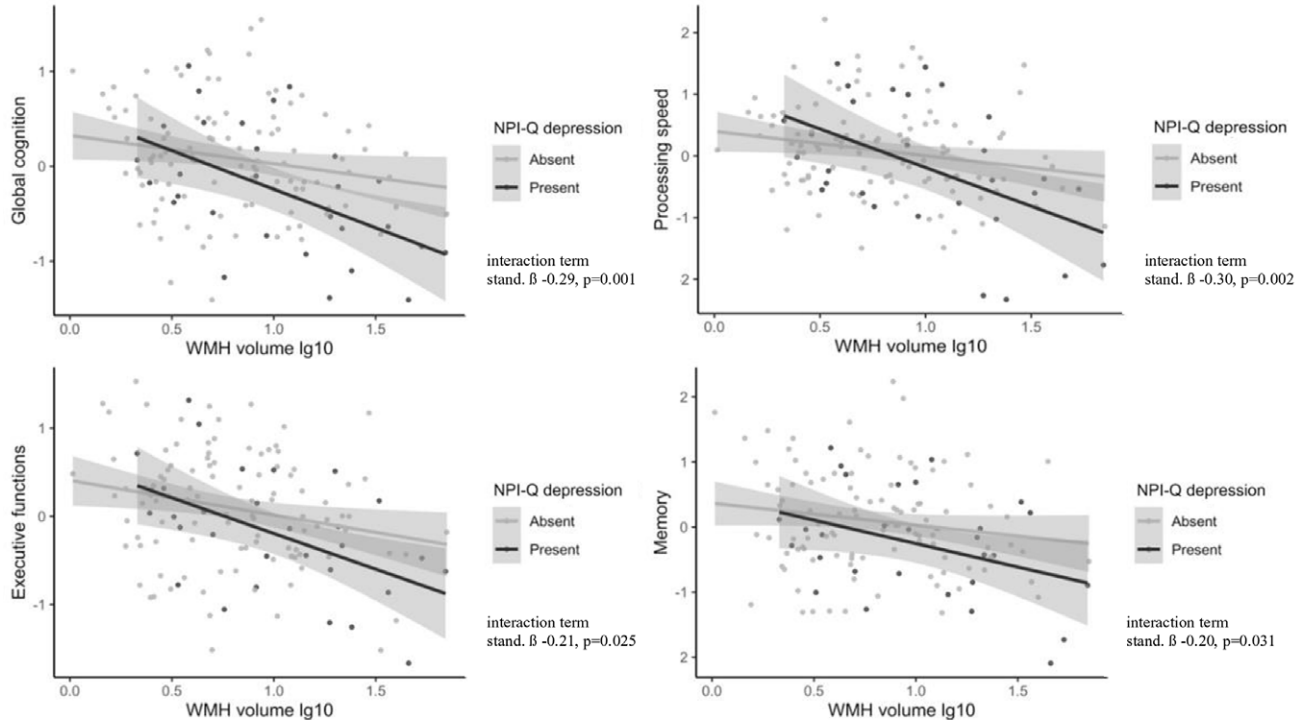

Figure 3. Interactions between white matter hyperintensity (WMH) volume and depressive symptoms group (based on the informant-evaluated Neuropsychiatric Inventory Questionnaire, NPI-Q) on cognitive functioning. Gray areas represent 95 % confidence intervals. All interactions were significant also after False Discovery Rate corrections.

performance irrespective of WMH severity. The other most common neuropsychiatric symptoms (irritability, night time disruptive behaviors, and changes in appetite) were not related to cognitive or functional outcomes.

https://doi.org/10.1017/S1355617722000480 Published online by Cambridge University Press

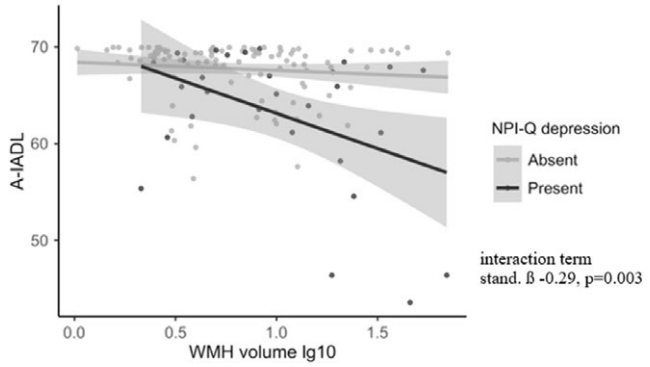

Figure 4. Interaction between white matter hyperintensity (WMH) volume and depressive symptoms group (based on the informant-evaluated Neuropsychiatric Inventory Questionnaire, NPI-Q) on functional abilities assessed with the Amsterdam Instrumental Activities of Daily Living questionnaire (A-IADL). Gray areas represent 95 % confidence intervals. Interaction was significant also after False Discovery Rate correction.

Previous meta-analyses have shown consistent associations between SVD brain pathology (WMH, lacunes, cerebral microbleeds, and stroke) and depression, apathy, fatigue, and delirium (Clancy et al., 2021; Rensma et al., 2018). In healthy individuals, there is tentative evidence with a small sample to suggest that WMH are related to significant preclinical neuropsychiatric symptoms (Spalletta et al., 2020). We also found evidence to suggest that WMH were related to the presence of neuropsychiatric symptoms, depressive symptoms in particular, already in covert SVD without presence of significant clinical impairment. In our study, the overall occurrence of neuropsychiatric symptoms was 38%, which is similar to what is found in mild cognitive impairment (MCI) research (Mariani, Monastero, & Mecocci, 2007).

Increasing neuropsychiatric symptoms have been previously shown to associate with SVD disease progression and cognitive decline over a 2-year period in a dementia-free elderly sample (Kan et al., 2020). Kan et al. found that at baseline, higher neuropsychiatric symptom incidence was associated with higher SVD-related brain pathology burden. The authors argued that neuropsychiatric symptoms could be used as a clinical marker of SVD progression. Our results were in line with these findings with significant associations between WMH volume and presence of neuropsychiatric symptoms. Furthermore, our results suggest that preclinical depressive symptoms accelerate worse cognitive impairment in covert SVD and are related to worse functional ability overall.

Previous research has identified differing results between apathy and depression in SVD. More precisely, apathy but not depression, has been shown to relate to white matter track connectivity and cognitive functioning (Hollocks et al., 2015; Lohner et al., 2017). Contrary to these previous results, we found depressive symptoms to be related to worse cognitive performance in the presence of higher levels of WMH, whereas apathy symptoms were related to worse cognitive outcomes irrespective of WMH. These previous studies used self-report questionnaires to determine the presence of apathy or depression. In our study, a close informant reported binary responses for each neuropsychiatric symptom. Neither of the evaluations represent a clinical diagnosis. The distinction between depressive and apathy symptoms in the NPI-Q is based on whether the subject seems sad or says they are depressed (depressive symptoms) or whether they seem less interested in their usual activities or in the activities and plans of others (apathy symptoms) according to the informant. Although we used solely the presence or absence of neuropsychiatric symptoms in our analyses, we still found significant associations, highlighting the importance of informant interviews already at an early stage of SVD assessments in order to get a more thorough view on a patient's ability to function.

Limitations of this study include the relatively small sample size. With a larger sample the occurrence of neuropsychiatric symptoms would be higher and there would be more statistical power to find possible effects of other, less common neuropsychiatric symptoms. It is also important to emphasize that this study is about neuropsychiatric symptoms and not about neuropsychiatric diagnoses. Symptom severity was predominantly evaluated low by the informants, suggesting that these symptoms might not reach the level required for a clinical diagnosis. Another limitation is the cross-sectional design, which only permits inferences of how the neuropsychiatric symptoms are related to WMH at one point in time. More research is needed to examine these relationships over time in covert SVD.

A meta-analysis in MCI has suggested that neuropsychiatric symptoms in the elderly might be an early sign of brain pathology and as such should be routinely screened (Martin & Velayudhan, 2020). Apathy and irritability in particular have been linked to Alzheimer's disease progression and cognitive decline. In Alzheimer's disease, WMH have been shown to associate with significant cognitive impairment and increase in depressive symptoms over time, whereas no relation to an increase in informant-evaluated neuropsychiatric symptoms has been found (Puzo et al., 2019). Our results were different from the aforementioned previous research possibly due to differences in our sample populations (Alzheimer's/SVD). We found neuropsychiatric symptoms to be present already in covert SVD and to have a significant role on subjects' cognitive and functional abilities. Due to the potential to use neuropsychiatric symptoms as an early sign for future decline, more longitudinal research is needed.

Considerable amount of research exists on the topic of the "vascular depression hypothesis", suggesting that cerebrovascular disease may "predispose, precipitate or perpetuate" some geriatric depressive syndromes (Taylor, Aizenstein, & Alexopoulos, 2013). Cognitive impairment in these cases is common and response to antidepressant medication is often poor. Taylor, Aizenstein and Alexopoulos (2013) have suggested a hypothesis, wherein a disconnection due to focal vascular damage and WMH location is crucial in the potential development of vascular depression symptomatology. More recent meta-analyses support the vascular cognitive hypothesis (Rensma et al., 2018; van Agtmaal et al., 2017). Our study gives tentative evidence to suggest these processes may commence already at the preclinical stages of SVD.

To conclude, we found that neuropsychiatric symptoms in general, and depressive symptoms in particular, associated with WMH, and importantly, seemed to accelerate cognitive impairment related to preclinical SVD. Especially depressive symptoms interact with WMH resulting in worse cognitive and functional abilities, whereas apathy relates to worse cognitive and functional outcomes irrespective of WMH. Our results imply a need to screen neuropsychiatric symptoms at an early stage of SVD assessment, as they are associated with worse cognitive and functional outcomes. Finally, our results highlight the importance of having an informant present at an evaluation, since even at the covert stage of SVD,

https://doi.org/10.1017/S1355617722000480 Published online by Cambridge University Press

an informant can aid in recognizing those patients that are at a higher risk for worse outcomes.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1355617722000480

Acknowledgments. We thank Dr. Sietske S. A. Sikkes, Department of Clinical, Neuro and Developmental Psychology, VU University; Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Amsterdam UMC, Amsterdam, The Netherlands, for providing the A-IADL scale, and Dr. Teemu Paajanen and Dr. Jussi Virkkala from the Research and Service Centre, Finnish Institute of Occupational Health, Helsinki, Finland, for providing the Flexible Attention Test, to the use of Helsinki Small Vessel Disease study.

Funding statement. The study was funded by the Helsinki and Uusimaa Hospital District, University of Helsinki and Päivikki and Sakari Sohlberg Foundation, Finland.

Conflicts of interest. JK and JL are shareholders at Combinostics Oy. JL has received lecture fees from Merck and Sanofi (paid to the employer). The other authors report no competing of interests.

References

Arola, A., Laakso, H. M., Pitkänen, J., Koikkalainen, J., Lötjönen, J., Korvenoja, A., Erkinjuntti, T., Melkas, S., & Jokinen, H. (2021). Associations of cognitive reserve and psychological resilience with cognitive functioning in subjects with cerebral white matter hyperintensities. *European Journal of Neurology*, *28*, 2622–2630. https://doi.org/10.1111/ene.14910

Brookes, R. L., Herbert, V., Lawrence, A. J., Morris, R. G., & Markus, H. S. (2014). Depression in small-vessel disease relates to white matter ultrastructural damage, not disability. *Neurology*, *83*, 1417–1423. https://doi.org/10.1212/WNL.0000000000000882

Chin, J., Seo, S. W., Kim, S. H., Park, A., Ahn, H.-J., Lee, B. H., Kang, S. J., and Na, D. L. (2012). Neurobehavioral dysfunction in patients with subcortical vascular mild cognitive impairment and subcortical vascular dementia. *Clinical Neuropsychologist*, *26*, 224–238. https://doi.org/10.1080/13854046.2012.658865

Clancy, U., Gilmartin, D., Jochems, A. C. C., Knox, L., Doubal, F. N., & Wardlaw, J. M. (2021). Neuropsychiatric symptoms associated with cerebral small vessel disease: A systematic review and meta-analysis. *The Lancet. Psychiatry*, *8*, 225–236.

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The neuropsychiatric inventory: Comprehensive assessment of psychopathology in dementia. *Neurology*, *44*, 2308–2314. https://doi.org/10.1212/wnl.44.12.2308

Du, J., Zhu, H., Zhou, J., Lu, P., Qiu, Y., Yu, L., Cao, W., Zhi, N., Yang, J., Xu, Q., Sun, J., & Zhou, Y. (2020). Structural brain network disruption at preclinical stage of cognitive impairment due to cerebral small vessel disease. *Neuroscience*, *449*, 99–115. https://doi.org/10.1016/j.neuroscience.2020.08.037

Geda, Y. E., Roberts, R. O., Knopman, D. S., Petersen, R. C., Christianson, T. J. H., Pankratz, V. S., Smith, G. E., Boeve, B. F., Ivnik, R. J., Tangalos, E. G., & Rocca, W. A. (2008). Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: Population-based study. *Archives of General Psychiatry*, *65*, 1193. https://doi.org/10.1001/archpsyc.65.10.1193

Hamilton, O. K. L., Backhouse, E. V., Janssen, E., Jochems, A. C. C., Maher, C., Ritakari, T. E., Stevenson, A. J., Xia, L., Deary, I. J., & Wardlaw, J. M. (2021). Cognitive impairment in sporadic cerebral small vessel disease: A systematic review and meta-analysis. *Alzheimer's & Dementia*, *17*, 665–685. https://doi.org/10.1002/alz.12221

Hollocks, M. J., Lawrence, A. J., Brookes, R. L., Barrick, T. R., Morris, R. G., Husain, M., & Markus, H. S. (2015). Differential relationships between apathy and depression with white matter microstructural changes and functional outcomes. *Editor's Choice*, *138*, 3803–3815. https://doi.org/10.1093/brain/awv304

Jokinen, H., Laakso, H. M., Ahlström, M., Arola, A., Lempiäinen, J., Pitkänen, J., Paajanen, T., Sikkes, S. A. M., Koikkalainen, J., Lötjönen, J., Korvenoja, A., Erkinjuntti, T., & Melkas, S. (2022). Synergistic associations of cognitive and motor impairments with functional outcome in covert cerebral small vessel disease. *European Journal of Neurology*. https://doi.org/10.1111/ene.15108

Jutten, R. J., Peeters, C. F. W., Leijdesdorff, S. M. J., Visser, P. J., Maier, A. B., Terwee, C. B., Scheltens, P., & Sikkes, S. A. M. (2017). Detecting functional decline from normal aging to dementia: Development and validation of a short version of the Amsterdam IADL Questionnaire. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *8*, 26–35. https://doi.org/10.1016/j.dadm.2017.03.002

Kan, C. N., Gyanwali, B., Hilal, S., Ng, K. P., Venketasubramanian, N., Chen, C. L.-H., & Xu, X. (2020). Neuropsychiatric correlates of small vessel disease progression in incident cognitive decline: Independent and interactive effects. *Journal of Alzheimer's Disease*, *73*, 1053. https://doi.org/10.3233/jad-190999

Kim, H. J., Kang, S. J., Kim, C., Kim, G. H., Jeon, S., Lee, J. M., Oh, S. J., Kim, J. S., Choe, Y. S., Lee, K. H., Noh, Y., Cho, H., Yoon, C. W., Chin, J., Cummings, J. L., Lee, J. H., Na, D. L., & Seo, S. W. (2013). The effects of small vessel disease and amyloid burden on neuropsychiatric symptoms: A study among patients with subcortical vascular cognitive impairments. *Neurobiology of Aging*, *34*, 1913–1920. https://doi.org/10.1016/j.neurobiolaging.2013.01.002

Knopman, D. S., Griswold, M. E., Lirette, S. T., Gottesman, R. F., Kantarci, K., Sharrett, A. R., Jack, Jr., C. R., Graff-Radford, J., Schneider, A. L. C., Windham, B. G., Coker, L. H., Albert, M. S., Mosley, Jr., T. H., & ARIC Neurocognitive Investigators. (2015). Vascular imaging abnormalities and cognition: Mediation by cortical volume in nondemented individuals: Atherosclerosis risk in communities-neurocognitive study. *Stroke*, *46*, 433–440. https://doi.org/10.1161/STROKEAHA.114.007847

Koikkalainen, J., Rhodius-Meester, H., Tolonen, A., Barkhof, F., Tijms, B., Lemstra, A. W., Tong, T., Guerrero, R., Schuh, A., Ledig, C., Rueckert, D., Soininen, H., Remes, A. M., Waldemar, G., Hasselbalch, S., Mecocci, P., van der Flier, W., & Lötjönen, J. (2016). Differential diagnosis of neurodegenerative diseases using structural MRI data. *NeuroImage Clinical*, *11*, 435–449. https://doi.org/10.1016/j.nicl.2016.02.019

Lohner, V., Brookes, R. L., Hollocks, M. J., Morris, R. G., & Markus, H. S. (2017). Apathy, but not depression, is associated with executive dysfunction in cerebral small vessel disease. *PloS One*, *12*, e0176943. https://doi.org/10.1371/journal.pone.0176943

Mariani, E., Monastero, R., & Mecocci, P. (2007). Mild cognitive impairment: A systematic review. *Journal of Alzheimer's Disease*, *12*, 23–35. https://doi.org/10.3233/JAD-2007-12104

Martin, E., & Velayudhan, L. (2020). Neuropsychiatric symptoms in mild cognitive impairment: A literature review. *Dementia and Geriatric Cognitive Disorders*, *49*, 146–155. https://doi.org/10.1159/000507078

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*, 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Okura, T., Plassman, B. L., Steffens, D. C., Llewellyn, D. J., Potter, G. G., & Langa, K. M. (2011). Neuropsychiatric symptoms and the risk of institutionalization and death: The aging, demographics, and memory study: Neuropsychiatric symptoms, institutionalization, and death. *Journal of the American Geriatrics Society*, *59*, 473–481. https://doi.org/10.1111/j.1532-5415.2011.03314.x

Pantoni, L., Basile, A. M., Pracucci, G., Asplund, K., Bogousslavsky, J., Chabriat, H., Erkinjuntti, T., Ferro, J. M., O'Brien, J. T., Scheltens, P., Visser, M. C., Wahlund, L.-O., Wallin, A., Fazekas, F., Hennerici, M., Waldemar, G., & Inzitari, D. (2004). Impact of age-related cerebral white matter changes on the transition to disability – The LADIS study: Rationale, design and methodology. *Neuroepidemiology*, *24*, 51–62. https://doi.org/10.1159/000081050

Prins, N. D., van Dijk, E. J., den Heijer, T., Vermeer, S. E., Jolles, J., Koudstaal, P. J., Hofman, A., & Breteler, M. M. B. (2005). Cerebral small-vessel disease and decline in information processing speed, executive function and memory.

Brain: A Journal of Neurology, *128*, 2034–2041. https://doi.org/10.1093/brain/awh553

Puzo, C., Labriola, C., Sugarman, M. A., Tripodis, Y., Martin, B., Palmisano, J. N., Steinberg, E. G., Stein, T. D., Kowall, N. W., McKee, A. C., Mez, J., Killiany, R. J., Stern, R. A., & Alosco, M. L. (2019). Independent effects of white matter hyperintensities on cognitive, neuropsychiatric, and functional decline: A longitudinal investigation using the National Alzheimer's Coordinating Center Uniform Data Set. *Alzheimer's Research & Therapy*, *11*, 64. https://doi.org/10.1186/s13195-019-0521-0

Rensma, S. P., van Sloten, T. T., Launer, L. J., & Stehouwer, C. D. A. (2018). Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, *90*, 164–173. https://doi.org/10.1016/j.neubiorev.2018.04.003

Spalletta, G., Iorio, M., Vecchio, D., Piras, F., Ciullo, V., Banaj, N., Sensi, S. L., Gianni, W., Assogna, F., Caltagirone, C., & Piras, F. (2020). Subclinical cognitive and neuropsychiatric correlates and hippocampal volume features of brain white matter hyperintensity in healthy people. *Journal of Personalized Medicine*, *10*, 172. https://doi.org/10.3390/jpm10040172

Steinberg, M., Shao, H., Zandi, P., Lyketsos, C. G., Welsh-Bohmer, K. A., Norton, M. C., Breitner, J. C. S., Steffens, D. C., Tschanz, J. T., & Cache County Investigators. (2008). Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: The Cache County study. *International Journal of Geriatric Psychiatry*, *23*, 170–177. https://doi.org/10.1002/gps.1858

Tay, J., Tuladhar, A. M., Hollocks, M. J., Brookes, R. L., Tozer, D. J., Barrick, T. R., Husain, M., de Leeuw, F.-E., & Markus, H. S. (2019). Apathy is associated with large-scale white matter network disruption in small vessel disease. *Neurology*, *92*, e1157–e1167. https://doi.org/10.1212/WNL.0000000000007095

Taylor, W. D., Aizenstein, H. J., & Alexopoulos, G. S. (2013). The vascular depression hypothesis: Mechanisms linking vascular disease with depression. *Molecular Psychiatry*, *18*, 963–974. https://doi.org/10.1038/mp.2013.20

van Agtmaal, M. J. M., Houben, A. J. H. M., Pouwer, F., Stehouwer, C. D. A., & Schram, M. T. (2017). Association of microvascular dysfunction with late-life depression: A systematic review and meta-analysis. *JAMA Psychiatry*, *74*, 729–739. https://doi.org/10.1001/jamapsychiatry.2017.0984

van Swieten, J. C., Koudstaal, P. J., Visser, M. C., Schouten, H. J., & van Gijn, J. (1988). Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*, *19*, 604–607. https://doi.org/10.1161/01.STR.19.5.604

Wang, Y., Catindig, J. A., Hilal, S., Soon, H. W., Ting, E., Wong, T. Y., Venketasubramanian, N., Chen, C., & Qiu, A. (2012). Multi-stage segmentation of white matter hyperintensity, cortical and lacunar infarcts. *NeuroImage (Orlando, Fla.)*, *60*, 2379–2388. https://doi.org/10.1016/j.neuroimage.2012.02.034

Wardlaw, J. M., Smith, E. E., Biessels, G. J., Cordonnier, C., Fazekas, F., Frayne, R., Lindley, R. I., O'Brien, J. T., Barkhof, F., Benavente, O. R., Black, S. E., Brayne, C., Breteler, M., Chabriat, H., Decarli, C., de Leeuw, F.-E., Doubal, F., Duering, M., Fox, N. C., … Dichgans, M. (2013). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet Neurology*, *12*, 822–838. https://doi.org/10.1016/S1474-4422(13)70124-8

Xu, X., Ang, S. L., Hilal, S., Chan, Q. L., Wong, T. Y., Venketasubramanian, N., Ikram, M. K., & Chen, C. L.-H. (2015). Association of neuropsychiatric symptoms and sub-syndromes with cognitive impairment in community-dwelling Asian elderly. *International Psychogeriatrics*, *27*, 1839–1847. https://doi.org/10.1017/S1041610215000976

https://doi.org/10.1017/S1355617722000480 Published online by Cambridge University Press