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ORIGINAL ARTICLE

Hypertension and white matter lesions are independently associated with apathetic behavior in healthy elderly subjects: the Sefuri brain MRI study

Hiroshi Yao[1], Yuki Takashima[1], Takahiro Mori[1], Akira Uchino[2], Manabu Hashimoto[1], Takefumi Yuzuriha[1], Yoshikazu Miwa[3] and Toshiyuki Sasaguri[3]

Apathy is defined as a syndrome of primary loss of motivation not attributable to emotional distress, intellectual impairment or consciousness disturbance. The aim of our study was to investigate the effects of vascular risk factors and silent ischemic brain lesions on apathetic behavior of community-dwelling elderly subjects. Brain MRI and other medical examinations were performed on 222 non-demented community-dwelling elderly subjects (96 men and 126 women, average age 70.1 years). The apathy group was defined as the most apathetic quintile determined by Starkstein's apathy scale. Silent infarction, deep white matter lesions (DWMLs) and periventricular hyperintensities were detected in 12.2, 39.2 and 22.5%, respectively. Linear regression analysis (Pearson) revealed that the scores on the apathy scale correlated slightly but significantly with logarithmically transformed scores of the Modified Stroop Test (r=0.135, P=0.045), but not with the Mini-Mental State Examination. The apathy group tended to have more high blood pressure (141.6/82.6 *vs.* 136.1/79.6 mm Hg), less prevalent hyperlipidemia (18 *vs.* 35%) and lower serum albumin. Multivariate analysis (the forward stepwise method of logistic analysis) revealed an independent correlation between the apathy and grade of DWMLs (odds ratio 1.826, 95% confidence interval (CI) 1.129–2.953 per grade) or diastolic blood pressure (DBP) (odds ratio 1.055, 95% CI 1.014–1.098 per mm Hg) after adjusting for possible confounders. The mean apathy scale score in the DBP≧90 mm Hg group was significantly lower (more apathetic) than that in the DBP<80 group (P=0.011, analysis of covariance). This study showed that hypertension and DWMLs are independently associated with apathy in healthy elderly subjects.
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INTRODUCTION

Hypertension is one of the major risk factors for vascular dementia or vascular cognitive impairment. The Hisayama Study showed that age, prior stroke episodes, systolic blood pressure and alcohol consumption were independent risk factors for vascular dementia.[1] Although the HYVET trial of lowering blood pressure in subjects aged 80 years or older was stopped early because of a substantial reduction in total mortality and stroke by the treatment, the meta-analysis of HYVET and three similar trials might support antihypertensive treatment to reduce the risk of incident dementia.[2] Epidemiological and clinical studies have established an association between cardiovascular disease and neuropsychiatric symptoms such as depression and apathy. In a population-based sample of incident Alzheimer's disease, an exploratory analysis showed that vascular factors such as hypertension and a history of stroke were associated with various neuropsychiatric symptoms, including apathy.[3] Apathy is defined as a syndrome of primary loss of motivation not attributable to emotional distress, intellectual impairment or consciousness disturbance.[4,5] Apathy is one of the most common neuropsychiatric symptoms present in 3.2% of the general population, 14.7% of subjects with mild cognitive impairment and 35.9% of subjects with dementia.[6]

Multiple lacunes and leukoaraiosis cause various neuropsychiatric symptoms[7–10] as well as cognitive impairment.[11–13] According to the vascular depression hypothesis, small vessel diseases such as silent brain infarction (that is, subcortical lacunes) and/or white matter lesions (WMLs) may disrupt frontal–subcortical circuits and generate depressive symptoms.[7] Apathy can be the clinical expression of a depressed state, but it is distinct from depression as a disorder of motivation rather than mood. The working group of Vascular Cognitive Impairment Harmonization Standards has recommended that measure of apathy would be important to include, detecting and quantifying apathetic personality changes, which are rather common early mani-

[1]Center for Emotional and Behavioral Disorders, National Hospital Organization Hizen Psychiatric Center, Saga, Japan; [2]Department of Radiology, Saitama Medical University International Medical Center, Saitama, Japan and [3]Department of Clinical Pharmacology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
Correspondence: Dr H Yao, Center for Emotional and Behavioral Disorders, Hizen Psychiatric Center, Mitsu 160, Yoshinogari, Kanzaki, Saga 842-0192, Japan.
E-mail: hyao@hizen2.hosp.go.jp
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festations of subcortical vascular disease.[13] However, no study so far has investigated the effects of 'silent' subcortical vascular lesions on apathetic behavior of healthy elderly subjects. Therefore, we examined the effects of vascular risk factors and silent ischemic brain lesions on an apathetic mental condition in community-dwelling people.

METHODS

Participants

Since 1997, we randomly contacted approximately 1200 inhabitants aged 40 years or older, living in the rural community of Sefuri village, Saga, Japan, through the village office, and completed a brain MRI study in 720 subjects. Between 2003 and 2007, 222 elderly subjects aged 60 years or older were examined using the Starkstein's apathy scale.[4] These subjects were living independently at home without apparent dementia. Anyone with symptomatic cerebrovascular diseases, brain tumor, malignant neoplasm and psychiatric disorders, including depression or a history of head trauma, was excluded. We did not experience participants with Parkinson's disease. The local ethics committee approved this study, and written informed consent was obtained from all participants.

Definition of vascular risk factors

Participants underwent a structured clinical interview, a neurological examination, general hematology tests, biochemistry tests and electrocardiograms. Blood pressure was measured in the sitting position by the standard cuff method after 5 min of rest. Vascular risk factors were defined as described earlier.[14] Briefly, arterial hypertension was considered present if a subject had a history of repeated blood pressure recordings above 140/90 mm Hg or the subject was being treated for hypertension. Diabetes mellitus was defined as fasting plasma glucose greater than 7.77 mmol l^{-1} and/or HbA1c greater than 6.0%, or an earlier diagnosis of diabetes mellitus. Hyperlipidemia was defined as total serum cholesterol concentration greater than 5.69 mmol l^{-1} or if the subject was being treated for hyperlipidemia.

Assessment of apathy and cognitive function

All subjects underwent the Mini-Mental State Examination as the standard screening test and Modified Stroop Test as a screen for frontal lobe impairment.[15] Depressive mood and insomnia was defined as 'always' or 'frequent' (more than sometimes) presence of these symptoms filled in a structured questionnaire. The terms of the Starkstein's scale[4] were translated into Japanese,[16] and we (internal medicine (HY), psychiatry (TY) and neurology (YT)) further discussed and corrected the minor details of language. Each item on the apathy scale was quantified on a visual analog scale in which one end of a 60-mm-long line is 'absolutely correct' and the other end is 'completely wrong' (Figure 1). Of the 14 questions on the apathy scale, item-total correlations of question nos. 3 and 11 were weak (r=0.45 and 0.46, respectively); other questions showed better correlation (r=0.55–0.72) with total score. Therefore, we excluded the scores of these two questions from the analysis. The subject was judged as having apathy if the total score was below the fifth quintile.

Assessment of MRI findings

The combination of T1WI, T2WI and fluid-attenuated inversion recovery (FLAIR) images is required to accurately detect both silent brain infarction and mild WMLs.[17,18] Therefore, T1-weighted (TR/TE=510/12 ms), T2-weighted (TR/TE=4300/110 ms)and FLAIR (TR/TI/TE=6750/1600/22 ms) images were obtained with a slice thickness of 6 mm, with a 1-mm interslice gap with a brain MRI (1.0T; Shimadzu, Magnex XP, Kyoto, Japan). Brain infarcts were shown as low signal intensities on T1-weighted images, and their size was 5 mm or larger (Figure 2). The WMLs were defined as isointense with normal brain parenchyma on T1-weighted images and as high signal intensity areas on T2-weighted images. We used the validated rating scale of deep WMLs (DWMLs) by Fazekas *et al.*[18]: Grade 0, absent; Grade 1, punctate foci; Grade 2, beginning confluence of foci; and Grade 3, large confluent areas. For periventricular hyperintensities, we determined the presence and severity (Grade 0, absent; Grade 1, pencil thin; Grade 2, smooth halo lining) using FLAIR images. All scans were reviewed independently by two authors (HY and AU) who were blinded to all clinical data. In the case of disagreement between the raters, a consensus reading was held.

Statistical analysis

All values were given as mean ± s.d. except for error bars in Figures 1 and 3. We used an SPSS software package (version 11; Chicago, IL, USA) for the statistical analysis. Normality of the distribution was tested with the Shapiro–Wilk statistics. For the univariate analysis, the t-test for continuous variables, the χ^2-test for categorical variables and the non-parametric Mann–Whitney u-test for variables with skewed distribution were used as appropriate. We chose the variables for entry into the multivariate analysis on the basis of the clinical and neuroradiological findings with P-values of <0.20 after univariate testing. Multivariate analysis was performed using the forward stepwise method of logistic analysis. The mean apathy scale score, adjusted for age, and grades of DWMLs were compared among the three blood pressure categories with analysis of covariance.

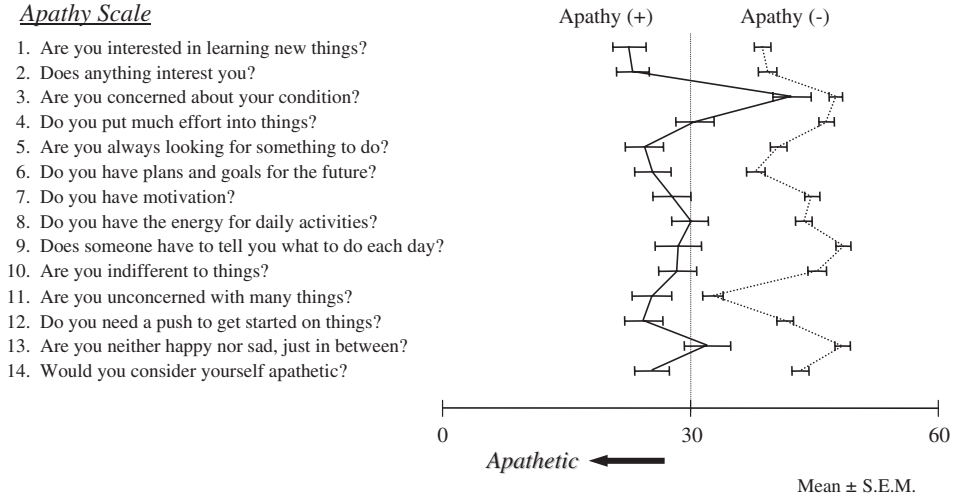

Figure 1 Starkstein's apathy scale and itemized scores of the groups divided by the lowest quintile of total scores. Each item on Starkstein's apathy scale[4] was quantified on a visual analog scale in which one end of a 60-mm-long line is 'absolutely correct' and the other end is 'completely wrong.' Participants marked where it is appropriate for each question, and then the distance was measured and counted as a score. In this study, we used the original arrangement in which the directions of the apathetic state were changed between question nos. 8 and 9, but this figure shows the left side as apathetic. The scores range from 0 to 720; lower scores indicate more severe apathy.

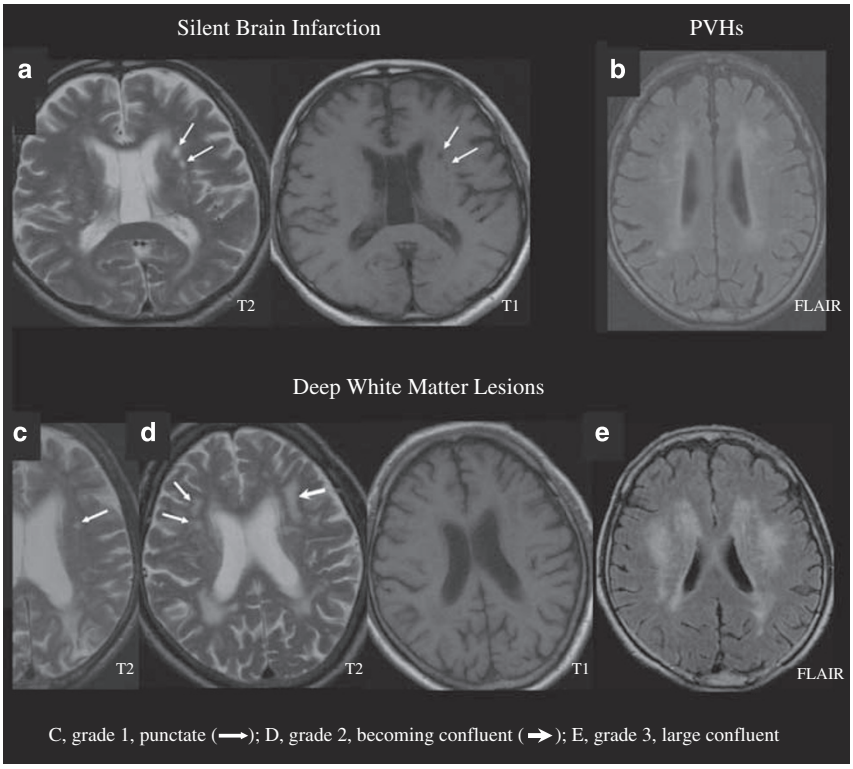

Figure 2 MRI of silent brain infarction (**a**), periventricular hyperintensities (PVHs) (**b**) and deep white matter lesions (**c**–**e**).

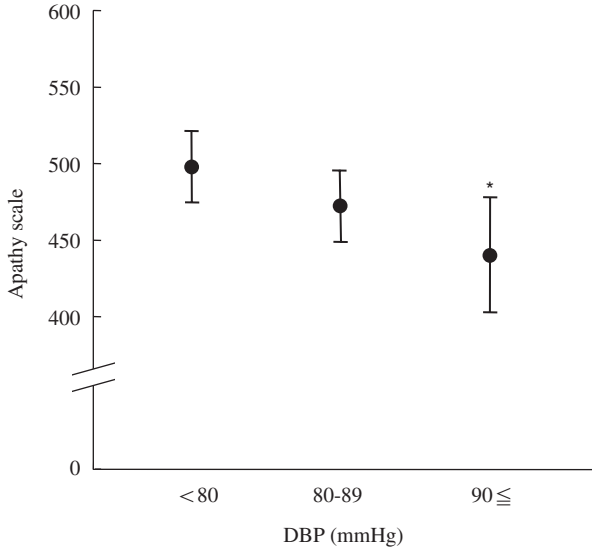

Figure 3 Apathy scale according to blood pressure category. Graph shows mean values and 95% confidence interval of apathy scale adjusted for age and the grade of deep white matter lesions. *P=0.011 *vs.* diastolic blood pressure (DBP) <80 mm Hg.

RESULTS

The subjects comprised 96 men and 126 women with a mean age of 70.1 years and a mean educational level of 10.2 years. Hypertension was present in 108 subjects. Blood pressure levels were 128.7 ± 14.4/78.2 ± 7.7, 144.2 ± 15.1/80.8 ± 10.2 and 163.3 ± 8.1/94.7 ± 4.7 mm Hg in normotensive subjects (n=114), treated hypertensive subjects (n=97) and non-treated hypertensive subjects (n=11), respectively. The prevalence of diabetes mellitus, hyperlipidemia and heart disease were 14.0, 32.0 and 4.5%, respectively. Silent brain infarction was detected by MRI in 26 subjects of 222 participants (12.2%). All except one infarction were small and deeply situated lacunar infarcts. DWMLs and periventricular hyperintensities were present in 87 (39.2%) and 50 (22.5%) subjects, respectively. Of the 87 subjects with DWMLs, small punctate (grade 1, n=62) lesions were the most prevalent followed by early confluent (grade 2, n=24) and large confluent (grade 3, n=1). DWMLs were more prevalent in the apathy group (55 *vs.* 35%) (Table 1).

The apathy scale appeared to have an almost normal distribution, but the Shapiro–Wilk test did not significantly support the normality (P=0.039) (Figure 4). The apathy group, defined as the most apathetic quintile determined by the apathy scale, tended to have more high blood pressure (141.6/82.6 *vs.* 136.1/79.6 mm Hg), less prevalent hyperlipidemia (18 *vs.* 35%) and lower serum albumin (41.5 ± 3.5 *vs.* 43.1 ± 3.4 g l^{-1}) (Table 1). Although the differences of Modified Stroop Test between the groups with or without apathy did not reach a statistical significance (P=0.093, Mann–Whitney u-test), linear regression analysis revealed that the apathy scale score correlated significantly with the logaristic-transformed score of Modified Stroop Test (r=0.135, P=0.045), but not with Mini-Mental State Examination. The prevalence of depressive mood and insomnia was not significantly different between the groups. When possible confounders were entered into the multivariate logistic regression model (the forward stepwise method), the independent predictors of apathy were diastolic blood pressure (DBP) (odds ratio (OR) 1.055; 95% confidence interval (CI) 1.014–1.098 per 1 mm Hg), hyperlipidemia (OR 0.371; 95% CI 0.153–0.901), albumin (OR 0.317; 95% CI 0.115–0.870 g^{-1} l^{-1}) and DWMLs (OR 1.826; 95% CI 1.129–2.953 per grade) (Table 2). The mean apathy scale score in the DBP≧90 mm Hg group was 439 (95% CI 402–477), which was significantly lower than

497 (95% CI 474–521) in the DBP < 80 group (P=0.011, analysis of covariance) (Figure 3).

DISCUSSION

This is the first study that showed that hypertension and DWMLs might contribute to apathy syndrome in healthy elderly people. Apathy was slightly but significantly associated with frontal lobe dysfunction but not with global cognitive function assessed with Mini-Mental State Examination. Apathetic subjects were not depressed in terms of the similar prevalence of depressed mood and insomnia with non-apathetic subjects. Subcortical vascular disease and DWMLs seen in community-dwelling subjects are associated with cognitive impairment or dementia, depression and gait disturbance.[7–9,11–13,19] Similarly, multiple lacunes cause frontal lobe dysfunction,[15] including a difficulty in shifting set, impaired executive functions, decreased verbal fluency and apathy. Apathy observed in this study might have occurred when the frontal cortex was functionally disconnected from relevant limbic input through basal ganglia by DWMLs.[20]

Small-vessel disease is the predominant cause of silent brain infarction and WMLs.[19] Apart from age, the main risk factors for WMLs are vascular risk factors, particularly hypertension. In our experience, although age was the major factor concerning both DWMLs and periventricular hyperintensities, hypertension was also but less robustly associated with WMLs (OR 1.6) compared with silent brain infarction (OR 3.2) (unpublished observation, abstract appeared in *Stroke* 2007; **38**: 535). In the Perindopril Protection Against Recurrent Stroke Study, the risk of new WMLs was reduced by 43% in the active antihypertensive treatment group, with a reduced blood pressure by 11.2/4.3 mm Hg compared with the placebo group.[21] Although patients vulnerable to hypotension are probably not well represented in earlier trials such as Perindopril Protection Against Recurrent Stroke Study, the treatment of vascular risk factors is all that physicians have at their disposal.[19] Furthermore, DBP related with apathy independent of WMLs and silent infarction in this study.

Table 1 Characteristics of study population with or without apathy

	Apathy (+) n=*44*	*Apathy (−)* n=*178*	P-*value*
Age (years)	71.4 ± 7.5	69.8 ± 7.3	NS
Sex (male/female)	16/28	80/98	NS
Body mass index (kg m^{-2})	23.8 ± 3.8	23.1 ± 3.4	NS
Education (years)	9.8 ± 1.9	10.3 ± 2.2	NS
Depressive mood (%)	7	8	NS
Insomnia (%)	25	16	NS
Mini-Mental State Examination	27.3 ± 2.3	27.9 ± 1.9	0.121
Modified Stroop Test (s)	34.9 ± 62.1	20.4 ± 15.3	0.093
Hypertension (%)	59	46	0.122
Systolic blood pressure (mm Hg)	141.6 ± 18.0	136.1 ± 17.0	0.058
Diastolic blood pressure (mm Hg)	82.6 ± 9.7	79.6 ± 9.3	0.052
Diabetes mellitus (%)	14	14	NS
Hyperlipidemia (%)	18	35	0.028
Heart disease (%)	2	4	NS
Alcohol (units per week)	4.6 ± 11.0	4.7 ± 8.5	0.085
Smoking (%)	18	20	NS
Hematocrit	0.40 ± 0.04	0.40 ± 0.04	NS
Albumin (g l^{-1})	41.5 ± 3.5	43.1 ± 3.4	0.008
Fasting blood glucose (mmol l^{-1})	5.57 ± 1.08	5.81 ± 1.8	NS
HbA1c (%)	5.1 ± 0.7	5.3 ± 0.7	NS
Total cholesterol (mmol l^{-1})	4.89 ± 1.01	5.09 ± 0.77	0.145
HDL cholesterol (mmol l^{-1})	1.43 ± 0.35	1.53 ± 0.4	0.134
Triglyceride (mmol l^{-1})	1.20 ± 0.58	1.22 ± 0.53	NS
Creatinine (μmol l^{-1})	59.7 ± 16.2	60.3 ± 18.8	NS
Uric acid (μmol l^{-1})	300 ± 40	312 ± 44	NS
Silent brain infarction (%)	18	11	0.173
Deep white matter lesions (%)	55	35	0.020
Periventricular hyperintensities (%)	30	21	NS

Abbreviation: NS, not significant.
Values are mean ± s.d.
NS, P>0.20.

Table 2 Logistic regression analysis of factors predicting apathetic behavior

	Univariate		*Multivariate*	
	P-*value*	P-*value*	*OR*	*95% CI*
Hypertension	0.124			
Systolic blood pressure (mm Hg)	0.060			
Diastolic blood pressure (mm Hg)	0.054	0.009	1.055	1.014–1.098
Hyperlipidemia	0.032	0.028	0.371	0.153–0.901
Total cholesterol (mmol l^{-1})	0.146			
HDL cholesterol (mmol l^{-1})	0.134			
Albumin (g l^{-1})	0.010	0.026	0.317	0.115–0.870
Silent brain infarction (number)	0.118			
Deep white matter lesions (grade)	0.024	0.014	1.826	1.129–2.953
Periventricular hyperintensities (grade)	0.121			

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio.

Stem-and-Leaf Plot

Frequency	Stem & Leaf
4	2 . **0033**
8	2 . **56668899**
16	3 . **0011223344444444**
37	3 . **55555555566666666**777778888888889999999
31	4 . 000111111111112222233333333444 4
36	4 . 555666666677777777777778888888999999999
23	5 . 01111122233334444444444
32	5 . 55555556666666666777777788899999
16	6 . 0000011112234444
14	6 . 55555577788899
5	7 . 00112

Stem width : 100
Each leaf : 1 case (s)

Figure 4 Stem-and-leaf plot of apathy scale. The scores for apathy group defined as the most apathetic quintile are shown in bold.

Hypertension causes impaired cerebral microcirculation[22] or breakdown of the blood–brain barrier,[23] which may contribute to the development of cognitive impairment. In chronic hypertension, both the lower and upper limits of cerebral blood flow autoregulation are shifted toward a higher blood pressure as a result of structural alterations in small arteries.[24] Consequently, the hemodynamic reserve in hypertensive individuals is reduced, which predisposes hypertensives to circulatory insufficiency in the brain,[25] and possible brain dysfunction including cognitive impairment and apathy. Taken together, on the basis of facts on the treatable nature of hypertension and WMLs, it should be emphasized that apathy associated with hypertension and/or DWMLs in the general population is considered to be potentially preventable.

The limitation of this study would be that the apathy group was operationally defined by the self-rating apathy scale, and the clinical diagnosis of apathy was not confirmed by using a psychiatric structured interview. We asked five experienced psychiatrists how an assumed 'average' apathetic patient with moderate symptoms would score on this apathy scale, and we found that the upper limit (that is, mean+2 s.d.) of the five scores was 320 (unpublished observation). In this study, the mean score of the apathy group was 321 ± 46 (s.d.). Therefore, we could have detected a mild apathetic behavior in healthy elderly subjects, using the apathy scale modified as an analog visual scale.

Although our exploratory analysis found that lower levels of serum albumin and cholesterol were independently associated with apathy, the cause–result relationship of this altered nutritional status and apathy is not clear from the present cross-sectional analysis. Apathy might interfere with eating behavior, resulting in the $1.6\,g\,l^{-1}$ lower albumin and lower prevalence of hyperlipidemia (18 *vs.* 35%). Low serum albumin levels are observed in association with protein–energy malnutrition or non-thyroidal illness syndrome commonly seen in various illnesses. However, the albumin levels in our subjects were much higher than those in the cases reported by Hama *et al.*[26] Alternatively, apathetic behavior-altered food intake could contribute to the development of DWMLs as a consequence of insufficient nutrients, such as decreased plasma tryptophan, which we earlier suggested as one of the causative factors for DWMLs.[27,28] However, these possibilities remain only speculative, and these associations may be of interest in a future study.

In conclusion, this study showed that DWMLs and high blood pressure might contribute to apathy in healthy elderly subjects. This apathetic tendency was not related to age, global cognition or depressive symptoms. The intervention directed at hypertension and prevention of silent ischemic brain lesions, particularly DWMLs, would be beneficial to attenuate the motivation loss in healthy elderly subjects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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