Estimated Brain Age in Healthy Aging and Across Multiple Neurological Disorders

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Running Title： 3D T1WI of aging and neurological disorders

Purpose: To characterize brain aging in the above conditions and its clinical relevance.

Study Type: Retrospective.

Population: A total of 2913 healthy controls (HC), with 1395 females; 331 multiple sclerosis (MS); 189 neuromyelitis optica spectrum disorder (NMOSD); 239 Alzheimer’ s disease (AD); 244 Parkinson’s disease (PD); and 338 cerebral small vessel disease (cSVD).

Field Strength/Sequence: 3.0 T/Three-dimensional (3D) T1-weighted images.

Assessment: The brain age was estimated by our previously developed model, using a 3D convolutional neural network trained on 9794 3D T1-weighted images of healthy individuals. Brain age gap (BAG), the difference between chronological age and estimated brain age, was calculated to represent accelerated and resilient brain conditions. We compared MRI metrics between individuals with accelerated (BAG $\geqslant$ 5 years) and resilient brain age (BAG $\leq$ -5 years) in HC, and correlated BAG with MRI metrics, and cognitive and physical measures across neurological disorders. Statistical Tests: Student’s t test, Wilcoxon test, chi-square test or Fisher’s exact test, and correlation analysis. $P < 0.05$ was considered statistically significant.

Results: In HC, individuals with accelerated brain age exhibited significantly higher white matter hyperintensity (WMH) and lower regional brain volumes than those with resilient brain age. BAG was significantly higher in MS (10.30 ± 12.6 years), NMOSD (2.96 ± 7.8 years), AD (6.50 ± 6.6 years), PD (4.24 ± 4.8 years), and cSVD (3.24 ± 5.9 years) compared to HC. Increased BAG was significantly associated with regional brain atrophy, WMH burden, and cognitive impairment across neurological disorders. Increased BAG was significantly correlated with physical disability in MS ($r = 0.17$).

Data Conclusion: Healthy individuals with accelerated brain age show high WMH burden and regional volume reduction. Neurological disorders exhibit distinct accelerated brain aging, correlated with impaired cognitive and physical function.

Level of Evidence: 4

Technical Efficacy: Stage 2

Plain Language Summary

Estimated brain age, derived from neuroimaging using the deep learning method, serves as an indicator of brain health in both healthy individuals and those with various neurological disorders. Estimated brain age can identify asymptomatic individuals with older-appearing brains, linked to higher burdens of white matter hyperintensities and volume reduction of specific brain regions in the general population. Neurological disorders, including multiple sclerosis, neuromyelitis optica spectrum disorder, Alzheimer's disease, Parkinson's disease, and cerebral small vessel disease, exhibit varying degrees of deviation from the normal aging trajectory and accelerated brain aging, implying poorer cognitive function and more severe physical impairments.

Introduction

Age is an important risk factor for neurological disorders(1). Inflammatory demyelinating diseases, including multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD), tend to be more common in younger people(2), whereas neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and cerebral small vessel disease (cSVD), are more prevalent in older people (3-5). These five neurological disorders are closely associated with age regarding the initial presentation and disease duration.

Additionally, brain aging in diseased-free people is heterogeneous. Age-related brain changes may result in different trajectories of cognitive impairment and different burdens of MRI white matter hyperintensities (WMH) (4). Therefore, it is important to identify individuals who deviate from normal aging at a given age (5). However, aging is a complex and multifactorial process influenced by genetic, environmental, and stochastic factors. Aging does not affect people uniformly, leading to different age-health trajectories (6, 7). Chronological age can serve as a basic benchmark but may fail to capture the aging process fully. In contrast, biological age may more accurately reflect the aging process and its associations with age-related diseases and lifespan(8).

Estimated brain age derived from MR images is considered a form of biological age, serving as a robust index of the complex and multidimensional alterations occurring throughout the brain with aging(9, 10), which can be used to model trajectories of general brain health(11). The brain age gap (BAG) is defined as the difference between brain age and chronological age(12). A negative BAG indicates that the brain appears younger than expected, suggesting delayed brain aging, while a positive BAG indicates a brain age that is older than expected for the chronological age(10).

Estimated brain age determination has the potential to aid in identifying asymptomatic individuals who are experiencing atypical aging and could be at increased risk of future ill health(13). In healthy individuals, a BAG ≤ -5 years indicates resilience to brain aging, while a BAG ≥ 5 years can be considered to represent accelerated brain aging(9, 14). There is still insufficient research on the correlations between these aging patterns and changes in specific brain regions, white matter hyperintensity (WMH) burden, and cognitive function in both normal aging individuals and those with neurological disorders. Although Kaufmann and colleagues reported a range of people with psychiatric and neurological disorders exhibiting distinct patterns of brain aging(15), they did not examine the impact of WMH burden.

Here we aim to identify the MRI and clinical characteristics of advanced accelerated brain aging in healthy individuals and to explore brain aging patterns in patients with neurological disorders, including inflammatory demyelinating, neurodegenerative, and cerebrovascular diseases.

Materials and Methods

Participants

The study received ethical approval from the local ethics committee's institutional review board (Beijing Tiantan Hospital, Capital Medical University, No. KY-2019-050-02, KY-2019-140-02, and KY-2024-221-02), and each participant provided written informed consent in the local dataset. A cohort of 2,913 healthy controls (HC) was included from six centers in China from October 2020 to October 2022 and the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) dataset(16) (http://www.mrc-cbu.cam.ac.uk/datasets/camcan/) (Supplementary Table 1). HC subjects were defined as having no evidence of neurological or psychiatric disorders(17). The demyelinating patient cohort consisted of MS and NMOSD patients who were retrospectively selected from the above six centers in China from November 2009 to

April 2018 and prospectively recruited from Beijing Tiantan Hospital between December 2018 and September 2021 (Supplementary Table 1). In total, 331 MS patients and 189 AQP4+ NMOSD patients were selected in the current study. We retrospectively included AD, PD, and cSVD patients from Beijing Tiantan Hospital between December 2018 and October 2022. Two experienced neurology specialists (more than five years) made the diagnosis of neurological diseases in each center. Patients were excluded who met the following criteria: (a) a history of severe head injury or surgery and (b) a history of other disorders affecting the central nervous system. (c) poor quality T1-weighted imaging (T1w) and T2 fluid-attenuated inversion recovery (FLAIR) images(18). A flowchart of the included and excluded participants is shown in Fig. 1.

Clinical data

All participants' data were recorded: age, sex, and Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores. PD patients completed Hoehn and Yahr scale (HY) for disease severity (19) and the Movement Disorders Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS-III) score(20). Patients with MS and NMOSD, as well as some of HC also completed the Paced Auditory Serial Addition Task (PASAT), California Verbal Learning Test-Second Edition (CVLT-II), Brief Visuospatial Memory Test-Revised (BVMT-R), Symbol Digit Modalities Test (SDMT), and Expanded Disability Status Scale (EDSS), as shown in Fig.1.

Imaging

3D T1w images with 1 mm isotropic resolution and two- or three-dimensional FLAIR images were acquired using 3.0 T MRI systems from Philips Healthcare (Eindhoven, Netherlands), GE Healthcare (Milwaukee, WI, USA) and Siemens Healthineers (Erlangen, Germany). The system and acquisition parameter details are provided in Supplementary Table 2.

Imaging segmentation

Brain age and brain morphology were evaluated using 3D T1w images; WMH volume was evaluated using FLAIR images (n=2,873) (Supplementary Table 1).FLAIR images were segmented to quantify WMH volume using the Lesion Segmentation Tool version 3.0.0(21) (https://www.applied-statistics.de/lst.html). Brain segmentation was performed on 3D T1w images using FreeSurfer version 6.0.0 (22) (http://surfer.nmr.mgh.harvard.edu/) using the following approach: T1w images underwent automated cortical reconstruction, motion correction, intensity normalization, and intensity inhomogeneity correction and then were transformed and skull-stripped before normalization into Talairach space to obtain morphometric estimates. Cortical gray matter volumes were extracted using the Desikan–Killiany atlas and subcortical structures were segmented. Global MRI measures, including subcortical gray matter volumes (sGMV), cortical gray matter volumes (cGMV), cerebral white matter volumes (WMV), cerebrospinal fluid (CSF) and estimated total intracranial volumes (eTIV) were also extracted.

Brain age estimation model

The preprocessing steps for the 3D T1-weighted images included affine registration to Montreal Neurological Institute (MNI) space and skull stripping. The intensity of the registered images was normalized by dividing their signal intensity by the mean intensity within the cerebral mask. The scans were then resampled to 1 mm isotropic resolution using linear interpolation, serving as the input of the brain age estimation model (23). The brain age- estimation model we employed was based on a previous study that used deep learning to establish the model from 3D T1w images in a sample of 9,794 healthy individuals (23). This model achieved a mean absolute error of 2.63 years in the developmental validation set and demonstrated robustness across different scanners and centers(23). Brain age estimation is affected by age-

dependent biasand tends to be overestimated in younger individuals while underestimated in older individuals (24). Therefore, we applied the adjustment method to remove the dependency of BAG on chronological age and reduce uncertainty in BAG estimates (see Supplementary Materials) (25). In our next analysis, the estimated brain age was corrected.

Statistical analysis

Statistical analyses were conducted using R software version 4.1.3. Graphs were plotted using the ggplot2 package. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables were compared using the Student's t test and Wilcoxon test. Cohen's d effect sizes were calculated to examine group separation. Brain tissue volume, cognitive score, and WMH volume were compared between HC with accelerated brain aging (BAG ≥ 5 years) and those resilient to brain aging (BAG ≤ -5 years). Patients were compared with age- and sex-matched subsets of the HC group (ratio, 1:2) using the two-sample Wilcoxon test and Student's t test. Partial correlation analysis of BAG, cognitive scores, and WMH volume was performed in healthy individuals. Correlations of BAG with cognitive scores and EDSS scores in MS and AQP4+ NMOSD patients, as well as with HY stage and MDS-UPDRS-III in PD patients, were analyzed using Kendall's tau-b correlation, adjusting for age and sex. Correlations of BAG with MRI measurements were also assessed using Kendall's tau-b, adjusting for age, sex, and eTIV. False discovery rate (FDR) correction was applied in multiple comparisons. All statistical tests were two-sided. $P < 0.05$ was considered significant. Cohen's d values were categorized as follows: < 0.2 (negligible effect), 0.2 - 0.49 (small effect), 0.5 - 0.79 (moderate effect), ≥ 0.8 (large effect)(26).

Results

Participants and Brain Age Estimation Model

Overall, 4,254 individuals were included (mean age, 50.3 ± 15.2 years). The participants with neurological disorders comprised 1,341 patients (570 males and 771 females), including 311 with MS, 189 with NMOSD, 239 with AD, 244 with PD, and 338 with cSVD. The HC group comprised 2,913 participants (1,518 males and 1,395 females; Supplementary Table 3). Estimated brain age was significantly correlated with chronological age in this group (r = 0.97) (Supplementary Fig.1 and 2).

Comparison of MRI and clinical measures between HC with accelerated brain aging and those resilient to brain aging

There were 316 accelerated brain agers (mean chronological age: 49.33 ± 15.73 years) and 278 resilient brain agers (mean chronological age: 49.66 ± 14.48 years). There was no difference in sex or chronological age between the two groups (Supplementary Table 4). 60.25% (47/78) of cortical or subcortical regions exhibited lower volumes in accelerated brain agers (BAG ≥ 5 years) compared to resilient brain agers (BAG ≤ -5 years). The top three effect sizes (|Cohen's d|) of brain region volume alterations were in the left accumbens, right accumbens, and right ventral diencephalon (Cohen's d = −0.54, −0.53, and −0.37, respectively; pFDR <0.001). No brain regions showed higher volume in the HC with accelerated brain aging (Supplementary Table 5). Furthermore, WMH burden and CSF volume were significantly higher in HC with accelerated brain aging (see Supplementary Table 4). Global MRI measures (cGMV, sGMV and WMV), as well as all cognitive tests, did not significantly differ between the two groups.

BAG was significantly correlated with WMH volume (r = 0.18) (Supplementary Table 6) after adjusting for age and sex.

The BAG in age- and sex-matched healthy individuals and patients with neurological disorders

Compared with age- and sex-matched HC, brain age was significantly higher in both MS patients (mean BAG = 10.30 years; Cohen's d = 1.30; 95% CI, 1.15–1.45) and AQP4+ NMOSD patients (BAG = 2.96

years; Cohen's d = 0.63; 95% CI, 0.35–0.71; Fig. 2; Table 1). The difference in the BAG between MS and AQP4+ NMOSD patients was significant (Fig. 2a). Brain age was also significantly higher in AD patients (BAG = 6.50 years; Cohen's d = 1.13; 95% CI, 0.97–1.31) and PD patients (BAG = 4.24 years; Cohen's d = 0.90; 95% CI, 0.74–1.06) than in HC (Fig. 2; Table 1). Similarly, brain age was significantly higher in cSVD patients than in HC (BAG = 3.24 years; Cohen's d = 0.60; 95% CI, 0.47–0.73; Fig. 2; Table 1). The effect sizes for the BAG were largest in MS patients (Fig. 2).

Correlations between increased BAG and MRI measurements in patients with neurological disorders

The regions with lower brain regional volumes related to higher BAG in the left and right hemispheres were approximately symmetrical in all patient groups (Fig. 3). Among the brain regions where volume correlated with BAG, the regions with the highest effect sizes, differed by diagnostic group. Increased BAG was most strongly associated with volume reduction in specific brain regions across different disorders: the right accumbens (r = -0.39) in MS patients, the left caudal middle frontal gyrus (r = -0.20) in NMOSD patients, the left inferior parietal gyrus (r = -0.26) in AD patients, the right pars orbitalis gyrus (r = -0.10) in PD patients, and the left thalamus (r = -0.18) in cSVD patients (Fig. 3).

As for global MRI measures, increased BAG in MS, AQP4+ NMOSD, AD, PD, and cSVD patients was significantly associated with reduced cGMV and sGMV. Decreased WMV was significantly associated with increased BAG in AD, cSVD and MS patients but not in PD or AQP4+ NMOSD patients (Fig. 4).

WMH volumes were higher in all neurological disorder patients than in age- and sex-matched HC; the effect size was largest for MS patients (Cohen's d = 1.06), followed by cSVD patients (Cohen's d = 0.70) and AD patients (Cohen's d = 0.68; Supplementary Table 7). WMH volume was significantly correlated with BAG in all disease groups, as shown in Fig. 4.

Correlations between increased BAG and clinical scores in patients with neurological disorders

In MS patients, increased BAG was significantly associated with MoCA, PASAT, and SDMT scores (r = −0.18, −0.14, and −0.24, respectively). Increased BAG was significantly correlated with worse scores on MMSE in AQP4+ NMOSD patients (r = −0.13). Increased BAG was significantly associated with worse physical disability (i.e., EDSS scores) in MS patients (r = 0.17) but not AQP4+ NMOSD patients (r = 0.08; pFDR = 0.13). In AD patients, increased BAG was significantly linked to lower scores on MMSE and MoCA (r = −0.21 and −0.23, respectively). No correlation was found between MMSE and MoCA scores and BAG in PD patients (r = −0.003 and −0.04, respectively; pFDR > 0.05). No correlation was found between HY scale and MDS-UPDRS-III scores and BAG in PD patients (r = −0.01 and −0.09, respectively; pFDR > 0.05). Increased BAG was significantly associated with lower scores on MoCA in cSVD patients (r = −0.16; Fig. 4).

Discussion

In this study, we used the brain age estimation paradigm and investigated the brain age gap in large groups of healthy individuals and patients with neurological disorders. Healthy individuals with accelerated brain aging exhibit higher white matter hyperintensity burden and lower regional brain volumes, especially in deep gray matter. Brain age has the potential to serve as a screening tool to identify asymptomatic individuals with accelerated brain aging, suggestive of a higher risk of poor health outcomes. In addition, our results indicate varying degrees of deviation from normal aging, with the following disorders ranked in descending order of deviation: MS, AD, PD, cSVD, and AQP4+ NMOSD. BAG varied among patients with neurological disorders and was associated with brain atrophy in specific regions and WMH burden. Deep gray matter (e.g., the accumbens and thalamus) showed atrophy associated with increased BAG in neurological disorders. Furthermore, higher BAG was significantly correlated with lower cognitive scores across multiple neurological diseases and with poorer disability in MS patients.

Comparison of MRI measurements and clinical scores in HC with accelerated brain aging and resilient brain aging

Compared with resilient brain agers (BAG less than -5 years), advanced brain agers (BAG more than +5 years) showed widespread volume reduction of cortical or subcortical regions, with the large effect size seen in the deep gray matter nuclei (such as the accumbens, thalamus and amygdala). This volume reduction of brain regions, especially in the deep gray matter, impacts the acceleration of brain aging(27). It has been demonstrated that the nucleus accumbens and amygdala exhibit the steepest rates of volume loss during normal aging(28). Therefore, it can be inferred that the difference in deep gray matter nuclei between accelerated brain agers and resilient brain agers may not be significant, as there is no difference in chronological age (49.33 ± 15.73 years vs. 49.66 ± 14.48 years). However, individuals with accelerated brain aging showed reduced deep gray matter nuclei, particularly in the accumbens. This suggests structural alterations associated with accelerated brain aging occurred earlier than expected. This finding supports that brain age can be used as a screening tool to identify individuals with accelerated brain aging(10), though longitudinal validation is still needed. The volume of WMH increases with BAG, controlling for the effects of age and sex, indicating that WMH also promotes accelerated brain aging, which is consistent with previous studies(9, 29, 30). Brain age can capture subtle and widespread changes in the structure of the brain, both in clinical and population-based samples(10).

Our findings indicate that BAG is not linked to cognitive function in healthy participants, which is inconsistent with previous studies(9, 15). Brain plasticity can protect against aging and brain reserve may protect against cognitive impairment(31). Thus, even with increased brain age, individuals may still be within the “normal” cognitive range for their chronological age. Moreover, differences in cognitive ability

were not observed between the accelerated and resilient brain agers, suggesting that brain structural changes may precede cognitive impairment in the general population.

Correlations between BAG and MRI measurements and clinical scores across neurological disorders

Neurological diseases exhibited distinct patterns of accelerated aging despite other unexplained contributing factors (10). Identifying age-related diseases can help identify individuals at risk for poor health outcomes, as the aging process and disease processes often interact. With progression or conversion from a clinically isolated episode to MS(32) and from mild cognitive impairment to AD(33, 34), the BAG increases. Baseline BAG was an independent predictor of worsening EDSS in both NMOSD and MS(23), as well as the progression of cognitive impairment in AD(33, 34). The BAG in all disease groups was significantly associated with cGMV and sGMV, which agrees with previous reports(35, 36) and indicates that reduction in gray matter is a major factor contributing to a higher BAG. The brain regions that exhibit atrophy (e.g., the accumbens and thalamus) affect cognitive domains that are commonly affected in MS, AQP4+ NMOSD, AD and cSVD patients(37). These deep gray matter alterations are a hotspot for both age- and disease-related changes(10), as they were observed in healthy individuals with accelerated brain aging as well.

Distinct spatial patterns of BAG-related atrophy associations were observed across neurological diseases, which provide insight into the underlying pathological processes. The atrophied brain regions associated with BAG involve a wide range of cortical and subcortical nuclei, particularly the putamen, accumbens, and thalamus in MS patients. The deep gray matter, specifically the thalamus, experiences a fast decline, which leads to worsening disability in MS patients(38), and BAG was a predictive biomarker of physical ability in MS patients(39). The atrophy associated with BAG in MS patients is not only indicative of accelerated aging, but it is also linked to cognitive and physical abilities. This supports the clinical meaningfulness of brain age for potentially describing physical and cognitive abilities in MS patients.

Reduced regional volume in the left rostral middle frontal gyrus was mostly associated with the BAG, followed by deep gray matter nuclei in NMOSD patients. It has been shown that cortical atrophy of the middle frontal gyrus cortex, which has a low expression level of AQP4, is associated with cognitive impairment(39). Besides, gray matter atrophy, especially in deep gray matter, was only found in NMOSD patients with cognitive impairment(40). These cognitive-related structural changes in NMOSD patients support our results that higher BAG in AQP4+ NMOSD patients correlated with poor cognitive ability. In the current study, there was no association between BAG and EDSS scores in AQP4+ NMOSD patients, which contradicted the results obtained in the previous study(23). These inconsistent results may be attributed to differences in inclusion criteria and the heterogeneous nature of NMOSD patient groups. In addition, BAG increased faster than normal chronological aging in MS, with an additional 0.61 years of brain aging per year in a longitudinal study (32). Evidence indicates that, while MS and NMOSD share features like chronic inflammation, similar age groups, and large lesions with axonal loss, NMOSD typically does not show chronic progressive degeneration(41). This aligned with another study, which adjusted for sex, age at diagnosis, baseline EDSS, and normalized brain volume, finding that NMOSD patients' brains appear younger than those of MS patients(23). Although our results did not consider these adjustments, they were still consistent with these findings.

In AD patients, we observed a broader spectrum of atrophic regions compared to those with PD, which may have contributed to higher BAG values in AD patients. Similarly, a previous study showed that AD patients have a significantly "older-appearing" brain than PD patients(42). Accelerated brain age in PD (average: range from +0.75 to +2.9 years) was mild to moderate as compared with HC (42-44). AD patients showed marked deviation from normal aging patterns, which correlated with cognitive impairment (i.e., MMSE and MoCA scores), as reported in previous studies(33, 45). Our findings suggest that BAG in Parkinson's disease

(PD) patients did not show correlations with disease severity, cognitive function or motor symptoms, which partly contrasts with a previous study(44). Accelerated biological age was significantly related to disease duration, and worse cognitive and motor impairment but not to disease severity in PD patients(44). However, another study indicated a correlation between BAG based on white matter and MoCA scores ($r = -0.15$), while no correlation was found with MDS-UPDRS-III scores and disease duration adjusting for age and sex (42). Possible reasons for these discrepancies may include limited clinical data and few atrophic brain regions associated with BAG in PD patients in our study. We intend to expand the sample size in future studies to investigate the relationship between BAG and both motor and non-motor symptoms in PD patients. Structural alterations of the thalamus have been linked to cognitive impairment in cSVD patients(46), and cSVD patients with higher BAG may have poor cognition in our study, suggesting that the brain age estimated model can capture key brain region alterations. In addition, higher cSVD burden was associated with faster rates of cognitive impairment, implying that brain age has the potential to serve as a measure of cSVD burden and cognitive impairment.

There was a significant correlation between WMH volume and BAG values in all disease groups. Additionally, WMH volumes were associated with cognitive and clinical outcomes(47). This indicates that greater WMH burden may be associated with accelerated aging, reflecting a potential decline in brain health. Brain age and WMH burden reflect brain health from different yet complementary dimensions.(9).

Limitations

In this study, we included a large sample of healthy individuals and those with neurological disorders in the same brain age model. Our results revealed significant heterogeneity in brain aging in the general population, and accelerated aging observed across multiple neurological disorders. However, the study has several limitations. First, this was cross-sectional; future longitudinal studies of healthy individuals and patients with neurological disorders

are warranted to determine how the BAG changes over time and examine the association of the baseline BAG with a patient's clinical outcome. Second, WMH segmentation was performed using a mixture of 2D and 3D FLAIR images, with the latter being more reliable(48). Third, deep learning methods are a "black box", and the interpretability of brain age estimation needs further improvement. Fourth, we did not consider lifestyle and genetic factors, hormonal levels, or other risk factors influencing brain age. These factors may explain the heterogeneity of brain aging in healthy individuals(29). Distinguishing changes in brain function and structure due to normal aging from those caused by neurological diseases is challenging. Fifth, the cognitive and clinical assessments implemented were relatively limited. Further studies are warranted to address comprehensive clinical and cognitive measures. Sixth, while we sought to include a diverse range of diseases, this inevitably results in a broad spectrum and heterogeneity, complicating the ability to conduct comprehensive analyses and discussions within the scope of this study. Future studies could focus on more targeted patient selection to better assess the impact of different diseases.

Conclusions

Within the uniform framework of the brain age estimation model, individuals with accelerated brain aging (BAG $\geq$ 5 years) exhibit higher white matter hyperintensity burdens and volume reduction in specific brain regions in the general population, which helps identify individuals at age-related risk. Furthermore, neurological disorders show varying degrees of deviation from the trajectory of normal aging, most notably in AD and MS patients. Higher BAG implies lower cognitive scores across various neurological diseases and greater disability in MS patients.

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Table

Table 1. Patient characteristics of various neurological disorders and age- and sex-matched HC

Variables	HC	MS	P value	HC	AQP4+ NMOSD	P value	HC	AD	P value	HC	PD	P value	HC	cSVD	P value
Number	624	331		374	189		411	239		471	244		648	338	
Age, mean (SD), y	37.0 (10.7)	36.2 (11.0)	0.264	43.4 (13.3)	43.1 (13.5)	0.84	67.1 (8.7)	68.1 (8.7)	0.16	59.7 (11.8)	60.0 (11.7)	0.68	59.9 (9.3)	60.4 (9.5)	0.405
Sex, female (%)	390 (62.5%)	211 (63.7%)	0.705	342 (91.4%)	173 (91.5%)	0.971	242 (58.9%)	145 (60.7%)	0.715	223 (47.3%)	119 (48.8%)	0.78	238 (36.7%)	123 (36.4%)	0.917
BAG, mean (SD), y	0.28 (3.6)	10.3 (12.6)	<0.001***	0.08 (3.7)	2.96 (7.8)	<0.001***	0.29 (4.0)	6.50 (6. 6)	<0.001***	0.25 (4.1)	4.24 (4.8)	<0.001***	0.23 (4.0)	3.24 (5.9)	<0.001***
Brain age, mean (SD), y	36.7 (11.0)	45.8 (16.5)	<0.001***	44.2 (13.2)	46.7 (15.6)	0.044*	66.9 (9.3)	73.9 (8.3)	<0.001***	60.0 (12.8)	64.2 (12.9)	<0.001***	60.1 (10.6)	63.5 (9.9)	<0.001***
Duration, median [IQR], m	NA	23.9[6,60.1]		NA	36.5[10,84]		NA	24.0[12,48]		NA	72.0[48,108]		NA	24.0[12,36]	
Relapses, median [IQR]	NA	2.0[1,4]		NA	2.0[1,4]		NA	NA		NA	NA		NA	NA	
MMSE, median [IQR]	30.0 [29,30]	29.0[27, 29.5]	<0.001***	30.0[29, 30]	29.0[27, 30]	0.001***	29.0[28 ,29]	18.0 [11,24]	<0.001***	29.0[28,29]	26.0[24,28]	<0.001***	29.0[28,29]	23.0[17.27]	<0.001***
MoCA, median [IQR]	28.0[25 ,29]	27.0[24, 28]	0.036*	27.0[24, 29]	26.0[22, 28]	0.042*	24.0[22 ,27]	13.0[6, 19]	<0.001***	23.0[22,26]	22.5[19,25]	<0.001***	24.0[22,26]	20.0[16,24]	0.011*
SDMT, median [IQR]	65.0[62 ,72.25]	50.0[38. 8,56.3]	<0.001***	65.5[62. 5,68.5]	41.0[30. 9,52.3]	<0.001***	NA	NA		NA	NA		NA	NA	
CVLT-II, median [IQR]	115[87. 5,129.5]	72.0[59, 98]	<0.001***	129[107. 8,135]	77.0[54, 100]	<0.001***	NA	NA		NA	NA		NA	NA	
PASAT, median [IQR]	54.0[50 ,59]	44.0[34. 3,49.8]	0.006**	NA	39.5[30, 47.8]	NA	NA	NA		NA	NA		NA	NA	
BVMT-R, median [IQR]	48.0[34 .3,58]	37.0[27, 50]	0.004**	57.0[46. 8,58]	34.0[24, 48]	0.005**	NA	NA		NA	NA		NA	NA	
HY, median [IQR])	NA	NA		NA	NA		NA	NA		NA	3.0[2.5 ,3.0]		NA	NA	
MDS-UPDRS-III, median [IQR]	NA	NA		NA	NA		NA	NA		NA	43.0[35,54]		NA	NA	
EDSS, median [IQR]	NA	2.25[1.5, 3.5]		NA	3.5[2.5,5 .0]		NA	NA		NA	NA		NA	NA	

cGMV, mean	**481.6(5**	**452.0**	**<0.00**	**458.8**	**430.09(4**	**<0.00**	**436.4**	**391.3**	**<0.00**	**453.4**	**444.3**	**0.032**	**454.0**	**439.0**	**0.032**
(SD), ml	**0.3)**	**(50.0)**	**1*****	**(44.8)**	**0.0)**	**1*****	**(45.4)**	**(47.7)**	**1*****	**(49.1)**	**(46.6)**	*****	**(44.6)**	**(45.9)**	*****
sGMV, mean	**58.8**	**53.0**	**<0.00**	**56.4**	**54.0**	**<0.00**	**53.5**	**50.3**	**<0.00**	**55.4**	**54.4**	**0.021**	**55.6**	**54.2**	**0.002**
(SD), ml	**(5.1)**	**(7.1)**	**1*****	**(4.7)**	**(5.0)**	**1*****	**(4.9)**	**(6.1)**	**1*****	**(5.2)**	**(5.7)**	*****	**(4.9)**	**(5.7)**	******
WMV, mean	**472.8**	**440.6**	**<0.00**	**451.5**	**439.9**	**0.011**	**441.4**	**419.3**	**<0.00**	**458.0**	**459.0**	**0.998**	**465.0**	**454.0**	**0.011**
(SD), ml	**(55.2)**	**(64.2)**	**1*****	**(50.6)**	**(46.8)**	*****	**(58.5)**	**(54.4)**	**1*****	**(61.0)**	**(60.1)**		**(58.2)**	**(61.5)**	*****
CSF, mean	**1009.1(**	**1342.6(4**	**<0.00**	**9964.4(2**	**1102.8(2**	**<0.00**	**1128.7(**	**1516.9**	**<0.00**	**1088.5**	**1220.0**	**<0.00**	**1123.4**	**1292.1**	**<0.00**
(SD), ml	**235.75)**	**17.0)**	**1*****	**12.3)**	**95.7)**	**1*****	**282.3)**	**(504.4)**	**1*****	**(261.3)**	**(295.4)**	**1*****	**(267.2)**	**(370.9)**	**1*****

Abbreviations: AD, Alzheimer's disease; AQP4+ NMOSD, aquaporin 4 antibody seropositive neuromyelitis optica spectrum disorders; BVMT-R, Brief Visuospatial Memory Test-Revised; CVLT-II, California Verbal Learning Test-Second Edition; EDSS, expanded disability status scale; HC, healthy controls; HY, Hoehn and Yahr scale; cGMV, cortical gray matter volume; sGMV, subcortical gray matter volume; MDS-UPDRS-III, Movement Disorders Society-Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; MS, multiple sclerosis; NA, not available; PASAT, Paced Auditory Serial Addition Task; PD, Parkinson's disease; SD, standard deviation; SDMT, Symbol Digit Modalities Test; WMV, white matter volume.

*p <0.05, **p <0.01, ***p <0.001

MMSE and MoCA scores were not adjusted for education on account of the lack of education information in most of the normal population.

Figure Legends

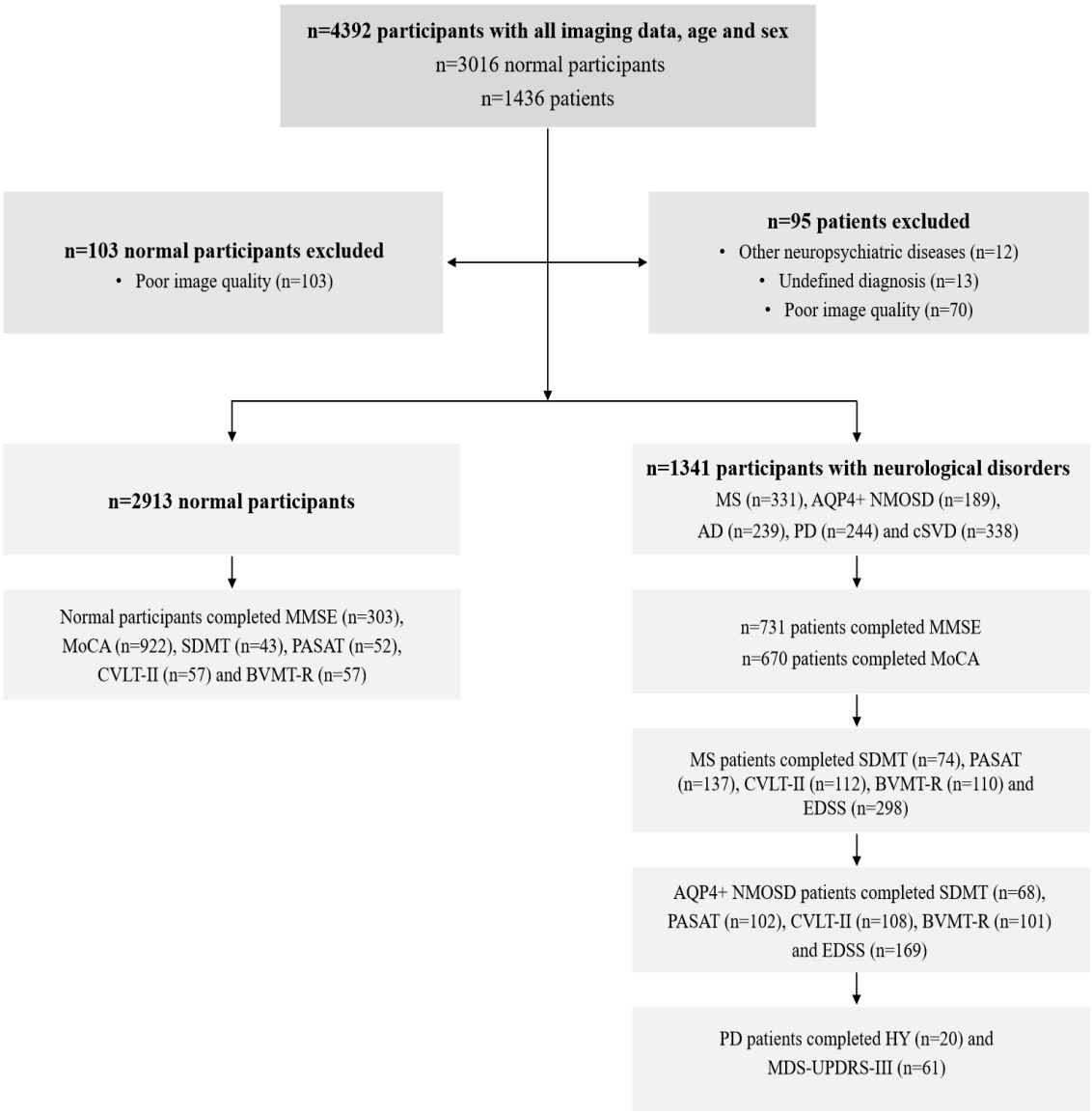

Fig. 1. Study flow chart.

Abbreviations: AD, Alzheimer's disease; AQP4+ NMOSD, aquaporin 4 antibody seropositive neuromyelitis optica spectrum disorders; BVMT-R, Brief Visuospatial Memory Test-Revised; CVLT-II, California Verbal Learning Test-Second Edition; EDSS, expanded disability status scale; HY, Hoehn and Yahr scale; MDS-UPDRS-III, Movement Disorders Society-Unified Parkinson’s Disease Rating Scale; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; MS, multiple sclerosis; PASAT, Paced

Auditory Serial Addition Task; PD, Parkinson's disease; SDMT, Symbol Digit Modalities Test; cSVD, cerebral small vessel disease.

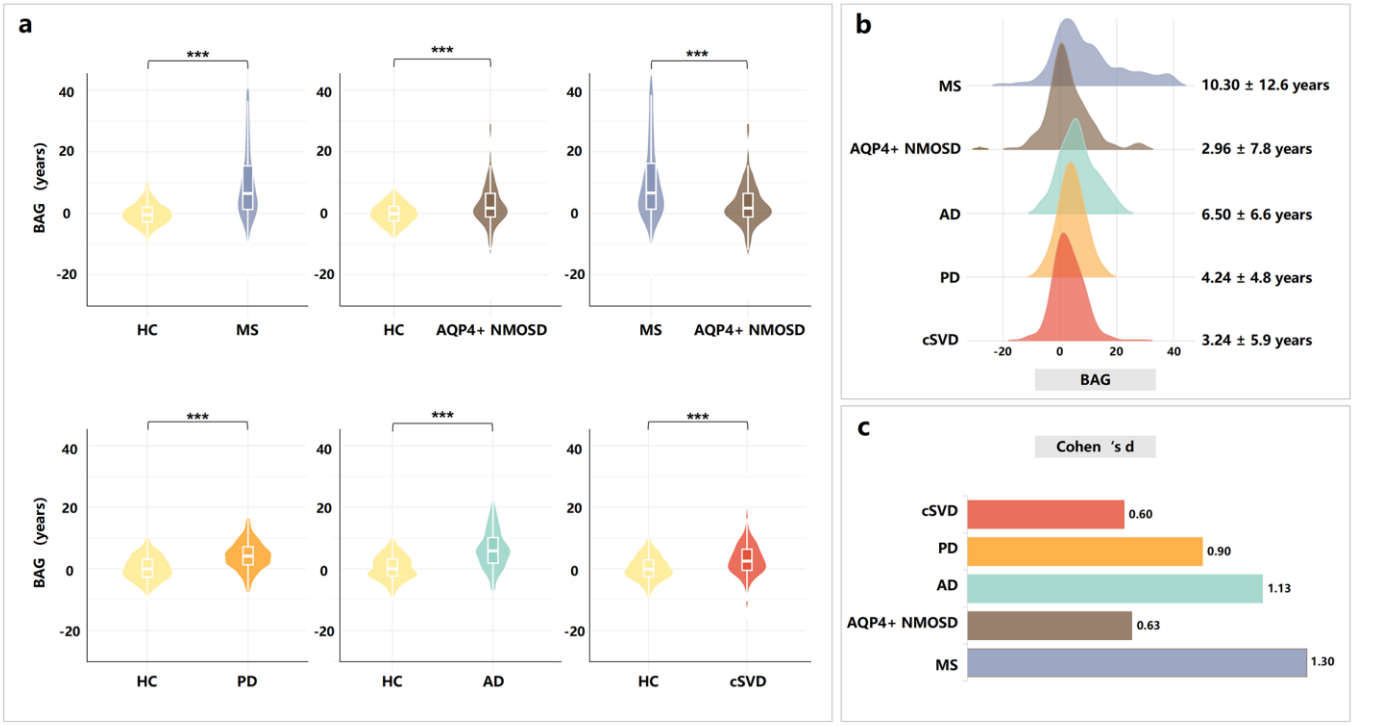

Fig. 2. BAG in various neurological disorders and age- and sex-matched HC.

(a) BAG in patients with MS, AQP4+ NMOSD, AD, PD, cSVD and HC. (b) Distribution of BAG and different accelerated brain aging among neurological disorders (c) Cohen's d effect sizes according to neurological disorders, compared with matched HC. *** $p<0.001$.

Abbreviations: AD, Alzheimer's disease; AQP4+ NMOSD, aquaporin 4 antibody seropositive neuromyelitis optica spectrum disorders; BAG, brain age gap; HC, healthy controls; MS, multiple sclerosis; PD, Parkinson's disease; cSVD, cerebral small vessel disease.

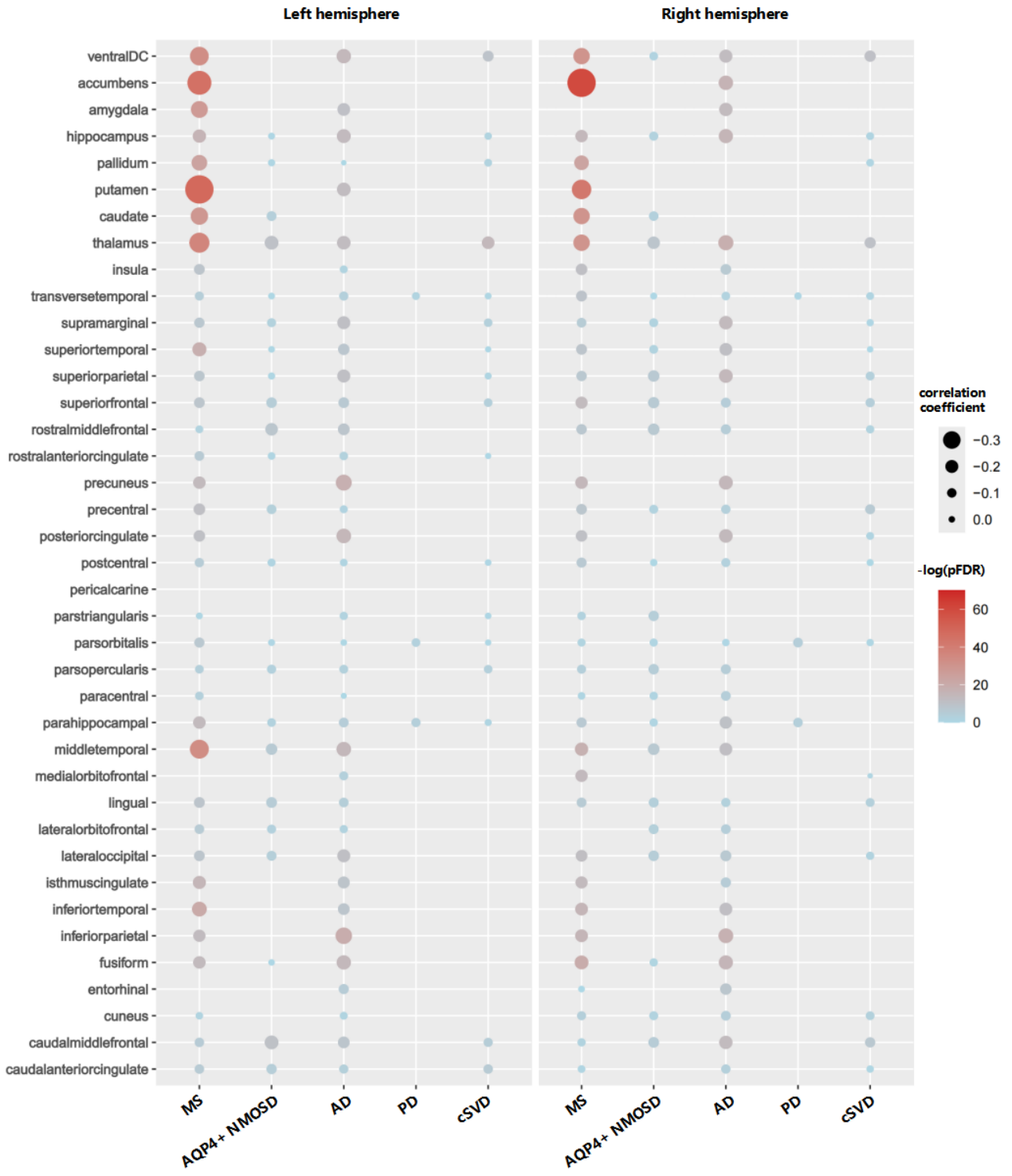

Fig. 3. Kendall's tau-b correlations between BAG and brain region atrophy in patients with neurological disorders.

Correlations between BAG and brain atrophy according to neurological disorders in the left and right hemispheres.

Abbreviations: AD, Alzheimer's disease; AQP4+ NMOSD, neuromyelitis optica spectrum disorder; MS, multiple sclerosis; PD, Parkinson's disease; cSVD, cerebral small vessel disease.

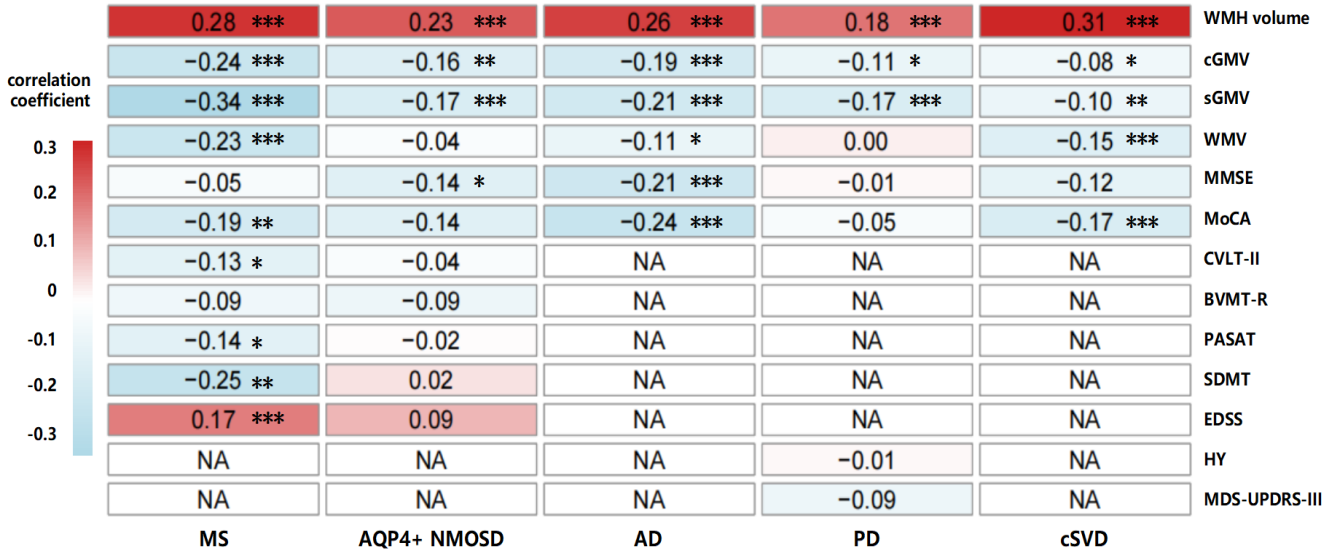

Fig. 4. Kendall's tau-b correlations among BAG, MRI measurements and clinical scores in patients with neurological disorders.

Abbreviations: AD, Alzheimer's disease; AQP4+ NMOSD, aquaporin 4 antibody seropositive neuromyelitis optica spectrum disorders; BVMT-R, Brief Visuospatial Memory Test-Revised; CVLT-II, California Verbal Learning Test-Second Edition; EDSS, expanded disability status scale; HY, Hoehn and Yahr scale; MDS-UPDRS-III, Movement Disorders Society-Unified Parkinson's Disease Rating Scale; cGMV, cortical gray matter volume; sGMV, subcortical gray matter volume; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; MS, multiple sclerosis; PASAT, Paced Auditory Serial Addition Task; PD, Parkinson's disease; SDMT, Symbol Digit Modalities Test; cSVD, cerebral small vessel disease; WMH, white matter hyperintensity; WMV, white matter volume.

*pFDR <0.05, **pFDR <0.01. ***pFDR <0.001; NA, not available; FDR, after false discovery rate correction.