Patterns of Focal Gray Matter Atrophy Are Associated With Bradykinesia and Gait Disturbances in Older Adults

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Objectives. Identify the neuroimaging correlates of parkinsonian signs in older adults living in the community.

Methods. Magnetic resonance imaging was obtained in 307 adults (82.9 years, 55% women, 39% blacks) concurrently with the Unified Parkinson Disease Rating scale—motor part. Magnetic resonance imaging measures included volume of whole-brain white matter hyperintensities and of gray matter for primary sensorimotor, supplementary motor, medial temporal areas, cerebellum, prefronto-parietal cortex, and basal ganglia.

Results. About 25% of the participants had bradykinesia, 26% had gait disturbances, and 12% had tremor. Compared with those without, adults with any one of these signs were older, walked more slowly, had worse scores on tests of cognition, mood and processing speed, and higher white matter hyperintensities volume (all $p \leq .002$). Gray matter volume of primary sensorimotor area was associated with bradykinesia (standardized odds ratio [95% confidence interval]: 0.46 [0.31, 0.68], $p < .0001$), and gray matter volume of medial temporal area was associated with gait disturbances (0.56 [0.42, 0.83], $p < .0001$), independent of white matter hyperintensities volume and age. Further adjustment for measures of muscle strength, cardiovascular health factors, cognition, processing speed, and mood or for gait speed did not substantially change these results.

Conclusions. Atrophy within primary sensorimotor and medial temporal areas might be important for development of bradykinesia and of gait disturbances in community-dwelling elderly adults. The pathways underlying these associations may not include changes in white matter hyperintensities volume, cognition, information processing speed, mood, or gait speed.

Key Words: Bradykinesia—Gait disturbances—Brain MRI.

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COMMUNITY-DWELLING elderly adults frequently experience generalized slowing of movements and gait/balance disturbances. These motor disturbances can occur in the absence of Parkinson's disease or other neurological conditions (1) and are more common with older age. Their prevalence is at least 15% in adults older than 65 years, and it can be as high as 50% among adults older than 80 years (2–4).

The onset of these common motor disturbances should be of concern because they are progressive and predict future falls, dementia, and death (1,5). Several studies have reported that common neurodegenerative conditions including Lewy bodies, nigral degeneration, amyloid plaques, neurofibrillary tangles, and cerebrovascular disease are related to gait

disturbance and other motor disturbances (1). However, these pathologies only explain a small portion of motor disturbances, suggesting that additional neurobiologic lesions may be important.

Although initial neuroimaging reports indicate a role for brain volume and white matter integrity (4,6,7), individual brain areas have not been thoroughly examined.

This study examines the relationship between gray matter volume of areas related to mobility, memory and processing speed with bradykinesia, gait disturbances, and tremor. Mobility-related areas in the frontal lobe, basal ganglia, and cerebellum are examined because of their known association with bradykinesia and gait disturbances (8). Memory and mood-related areas within the medial temporal lobe are also

of interest because of their association with spatial navigation and gait disturbances (9). Additionally, dementia and depression frequently accompany Parkinsonism (1,10,11). The processing speed area within prefronto-parietal cortices is also examined because of its associations with gait parameters (12,13). The contribution of neuroimaging markers to bradykinesia, gait disturbances, and tremor is tested in relation to other factors that can contribute to mobility: small vessel disease, brain function, muscle strength, and cardiovascular conditions.

METHODS

Study Population

Of 652 participants from the Health Aging and Body Composition Study at the Pittsburgh site (14) who were able to walk 20 m, 315 were interested and eligible for a brain 3.0-Tesla magnetic resonance imaging study in 2006–2007. Of these, 307 had complete data on the Unified Parkinson's Disease Rating scale and were free from Parkinson's disease. This study was approved by the University of Pittsburgh Institutional Review Board. A neuroradiologist examined each magnetic resonance imaging for abnormalities.

Magnetic Resonance Image

Acquisition and processing protocols have been published (15). Gray matter, white matter, and cerebrospinal fluid were segmented on skull-stripped T_1 -weighted images in native anatomical space (16), and volumes were estimated by summing voxels classified as these tissue types. Total intracranial volume was computed as the volume inside the inner skull. White matter hyperintensities volume (WMHv) was obtained from T_2 -weighted fluid-attenuated inversion recovery images using an automated region-growing method (17), the Johns Hopkins University Atlas (18), and normalized by brain volume. Neuroanatomical boundaries of gray matter regions were identified using a previously published atlas (19).

Assessment of Motor Disturbances

The Unified Parkinson's Disease Rating scale (20) was used to identify bradykinesia, tremor, and gait disturbances as previously described. Bradykinesia was present if slowing or hesitation was detected in either right or left extremities during finger tapping, fist clench, pronation–supination, or heel tapping. Gait disturbances were present if abnormality was detected for any one of the following: arising from a chair with arms folded across the chest, postural stability test (reduced response to sudden posterior displacement produced by pull on shoulders while subject is erect, with eyes open and feet slightly apart), posture (either moderately stooped and/or leaning on one side), or gait (either slowness, hesitancy, decreased arm swing, small amplitude, and poverty

of movement in general). Tremor of the upper extremities was rated as present if either facial or hand tremor was present at rest or during action. Tremor of the lower extremities was rated as present if it was detected either at rest or during action in either foot.

Other algorithms to classify bradykinesia, gait disturbances, and tremor were examined (1,2,7) in addition to the one applied (20); in internal validity analyses, the subgroups obtained after applying the algorithm by Louis et al. (7) were used.

Population Characteristics

Participants' gender, age, race, and whether or not they achieved a high-school level of education were examined. Presence of Parkinson's disease was ascertained from participant interview and confirmed by medical record. Systolic blood pressure (average of two measurements while sitting) was examined because of the documented association of hypertension with parkinsonian signs (21) and with neuroimaging markers (22). Muscle strength was quantified by isokinetic dynamometer with peak torque as summary measure (23); cardiovascular conditions were ascertained from participant interview and confirmed by medical record; overall cognition (Modified Mini-Mental Status score), mood (Center for Epidemiologic Studies—Depression score), processing speed (Digit Symbol Substitution Test), and mobility (time to walk) were tested using previously published protocols (24).

Statistical Analysis

In this cross-sectional analysis, mean gray matter volume (GMv) of each region/area was compared between groups (with/without bradykinesia, gait disturbances or tremor). The Sidak correction factor of $p = .002134$, with $\alpha = .05$ was used to correct for multiple comparisons among the seven brain areas. GMv that significantly differed between groups at $p < .002134$ in univariate analyses, subsequently entered logistic models with intracranial volume, small vessel disease, age, prevalent cardiovascular disease, stroke, and myocardial infarction. Other population characteristics that significantly differed between groups at $p < 0.1$ (using analyses of variance for continuous variable and chi-square for categorical variable) entered these logistic models as covariates. Standardized Z-scores of the neuroimaging markers were used. SPSS version 19.0 was used (IBM-SPSS Inc., Chicago, IL).

RESULTS

In this sample of 307 participants, 44% ($N = 133$) had bradykinesia, gait disturbances, or tremor, 25% had bradykinesia, 25% had gait disturbances, and 12% had upper extremity tremor (Table 1). Co-occurrence of bradykinesia and gait disturbances was observed in 34 participants

Table 1. Characteristics of the Sample Stratified by Presence/Absence of Parkinsonian Signs

		Presence of Bradykinesia, Gait Disturbances, or Tremor		
		All Cohort	Absent	Present
Number (%)		307		
Demographic	Age, years, mean (<i>SD</i>)	83 (2.83)	82.50** (2.56)	83.64 (3.04)
	Women, <i>N</i> (%)	180 (55)	100 (58.1)	75 (56.8)
	Black, <i>N</i> (%)	124 (39)	68 (39.5)	55 (41.7)
	Education $\geq$ HS, <i>N</i> (%)	155 (49)	89 (55.3)	61 (50.0)
Overall function	Quadriceps muscle strength, mean (<i>SD</i>)	82.07 (30.45)	84.77 (29.71)	78.34 (31.19)
	Modified Mini-Mental, mean (<i>SD</i>)	92.99 (6.62)	93.86* (6.23)	91.89 (6.96)
	Digit Symbol Substitution Test, mean (<i>SD</i>)	36.83 (13.31)	40.02** (12.42)	32.75 (13.35)
	CES-D, mean (<i>SD</i>)	6.91 (6.33)	5.93** (5.27)	8.14 (7.30)
	Time to walk 6 m, mean (<i>SD</i>)	1.00 (0.29)	1.08** (0.23)	0.91 (0.32)
Vascular risk factors and conditions	Systolic blood pressure, mmHg, mean (<i>SD</i>)	134.64 (19.59)	133.80 (18.97)	135.72 (20.38)
	Prevalence of diabetes, <i>N</i> (%)	79 (25.7)	41 (23.7)	38 (28.4)
	Prevalence of cardiovascular disease, <i>N</i> (%)	90 (29.3)	54 (31.2)	36 (26.9)
	Prevalence of stroke, <i>N</i> (%)	25 (8.1)	16 (9.2)	9 (6.7)
	Prevalence of myocardial infarct, <i>N</i> (%)	53 (17.3)	31 (17.9)	22 (16.4)
Markers of overall brain health	WMHv*, mean (<i>SD</i>)	0.61 (0.76)	0.48** (0.60)	0.76 (0.91)
	Atrophy†, number of voxels, mean (<i>SD</i>)	504686.52 (124094.50)	503289.16 (121822.41)	506524.5769 (127472.20)

Notes: CES-D = Center for Epidemiologic Studies—Depression; GMv = gray matter volume; HS = high school; WMHv = volume of white matter hyperintensities.

*Number of WMHv/number of voxels in brain $\times 100$.

†Space between the skull and the brain parenchyma. Higher values indicate higher total brain atrophy.

*Age-adjusted *p* value of between-group comparison is $\leq .01$. See text for *p* values. **Age-adjusted *p* value of between-group comparison is $< .002134$. See text for *p* values.

(11%). Lower-extremity tremor was nearly absent in this cohort ($n = 1$), and it was not examined further.

Compared with those without bradykinesia, gait disturbances or tremor, those with any one of these signs were older, had lower scores on tests of cognition, information processing speed and mood (higher Center for Epidemiologic Studies—Depression score), walked more slowly, and had greater WMHv ($p < .002134$ for all except for Modified Mini-Mental Status Exam: $p = .01$). By contrast, the distribution of race, gender, and other characteristics (Table 1) did not significantly differ between those with any one of these three signs as compared with those without ($p > .2$ for all). These differences were similar for bradykinesia, gait disturbances, and tremor (Supplementary Table 1). Additionally, muscle strength was significantly lower in those with gait disturbances as compared with those without (weight and age adjusted $p = .008$). Differences in age, Modified Mini-Mental score, and Center for Epidemiologic Studies—Depression score did not reach statistical significance for tremor ($p > .1$ for all) and differences in Modified Mini-Mental Status Exam score did not reach statistical significance for gait disturbances ($p = .1$).

Smaller GMv of primary sensorimotor area was associated with bradykinesia at $p < .002134$ and gait disturbances at $.002134 < p < .005$ but was not significantly associated with tremor ($p > .05$, Table 2). By contrast, smaller GMv of the medial temporal area was associated with gait disturbances at $p < .002134$ but not with bradykinesia or tremor ($p > .05$ for both, Table 2). Associations at $.002134 < p < .005$ were found between cerebellum and dorsolateral prefrontal cortex with bradykinesia ($p = .004$, Table 2), between

posterior parietal area and bradykinesia ($p = .004$) and gait disturbances at $p = .009$ ($p = .004$, Table 2), and also between the primary sensorimotor area and gait disturbances ($p = .005$, Table 2).

These associations had similar effect sizes and remained significant in fully adjusted models (Table 3). For each *SD* of GMv of the primary sensorimotor area (Table 3), there was a 54% difference in the probability of having bradykinesia. For each *SD* of GMv of memory-related regions (Table 3), there was a 40% age-adjusted difference in the probability of having gait disturbances. In these models, the association of WMHv with bradykinesia or gait disturbances was not significant (Table 3, Model 4).

Adjustment for scores on the Mini-Mental Test, Digit symbol Substitution, Center for Epidemiologic Study—Depression or for time to walk did not substantially attenuate the associations of sensorimotor or medial temporal areas with bradykinesia or gait disturbances, respectively (Table 3). Similarly, adjustment for muscle strength did not modify these associations (data not shown).

In secondary analyses, models were further adjusted for GMv of regions that were associated with the outcomes at $.0002134 < p < .05$. The association between GMv of the sensorimotor area with bradykinesia was marginally modified after adjustment for GMv of the cerebellum, dorsolateral prefrontal, and posterior parietal areas (standardized OR [95%CI], *p* value: .46 [0.28, 0.76], $p = .002$). The association of GMv of medial temporal area with gait disturbances was marginally modified after adjustment for GMv of primary sensorimotor and posterior parietal areas (0.60 [0.42, 0.86], 0.006).

Table 2. Mean and SD of Gray Matter Volume (voxel number) of Areas of Interest Are Reported for the All Sample and for Groups Stratified by Presence/Absence of Bradykinesia, Gait Disturbances, and Tremor

Brain MRI Measures	Bradykinesia		Gait Disturbances		Tremor	
	All Cohort	Absent	Present	Absent	Present	Absent
Sensorimotor cortex*	35830.60 (5621.07)	36597.45 (5589.20)	33499.78*** (5079.09)	36360.28 (5853.87)	34301.90** (4586.98)	35873.66 (5712.02)
Supplementary area	12871.48 (2286.90)	13016.95 (2406.36)	12429.30 (1821.28)	12985.45 (2301.21)	12542.54 (2226.75)	12825.76 (2274.50)
Basal ganglia†	14050.46 (4373.25)	14232.37 (4368.71)	13497.55 (4369.26)	14020.61 (3947.82)	14136.59 (5446.36)	13978.47 (4275.05)
Cerebellum	98939.23 (14190.77)	1000270.66 (14270.62)	94892.38** (13230.18)	99467.89 (14535.04)	97414.34 (13115.15)	99134.69 (14306.29)
Medial temporal lobe‡	26714.55 (3513.04)	26874.03 (3409.82)	26229.80 (3792.20)	27071.18 (3523.76)	25685.28*** (3291.69)	26762.61 (3549.30)
Dorsolateral prefrontal cortex§	26910.79 (3242.05)	27211.41 (3103.90)	25997.05** (3495.02)	27089.04 (3295.84)	26396.34 (3043.23)	27056.99 (3188.45)
Posterior parietal	43403.72 (6003.84)	43963.13 (5926.57)	41703.38* (5954.86)	43860.70 (6074.68)	42084.82* (5625.49)	43399.19 (5932.51)

Notes: MRI = magnetic resonance imaging.

*Includes the pre- and postcentral gyri.

†Includes thalamus, putamen, pallidum, and caudate.

‡Includes hippocampus, parahippocampus, amygdale, and entorhinal cortex, defined using the boundaries of the Brodmann area 28.

§Identified using the boundaries of the middle frontal gyrus.

||Includes precuneus, superior, and inferior posterior parietal cortex.

*p Value of between-group comparison is <.05 and above .005. **p Value of between-group comparison is ≤.005 and above .002135, the Sidak correction factor for multiple comparisons. ***p Value of between-group comparison is ≤.002135, the Sidak correction factor for multiple comparisons.

Results were similar when the classification of bradykinesia, gait disturbance, and tremor as described by Louis et al. was applied (data not shown).

DISCUSSION

The spatial distribution of neuroimaging markers appeared to be nonoverlapping for bradykinesia and gait disturbances. Among the neuroimaging markers examined, GMv of the primary sensorimotor area appeared to contribute more robustly to bradykinesia, but GMv of the medial temporal area appeared to contribute more robustly to gait disturbances. These associations remained independent of GMv of other regions as well as of other contributors of mobility, including small vessel disease, cardiovascular diseases and conditions, cognition, processing speed, mood, and muscle strength.

The association between motor-related regions and bradykinesia is consistent with our hypotheses. Activation within the motor network and within the sensorimotor area in particular has been previously reported (25). A functional imaging study of patients with Parkinson disease (PD) (26) indicates that lower activation of the sensorimotor area is related to bradykinesia. It is possible that smaller volume of this area, in adults free from PD, could explain the lower activation leading to movement slowing.

The association of smaller GMv of the medial temporal area with gait disturbances complements the growing literature on the association of memory and gait (eg, Markesbery [27]). Smaller volumes and microstructural abnormalities of the medial temporal network are strongly associated with memory problems, and these in turn are associated with gait (28). The contribution of hippocampal activity to locomotion has been supported by studies in animal models ever since the initial report of Vanderwolf (29). However, more recent neuroimaging reports in non-demented older adults (7,9), including our works (13,30), have yielded less consistent results. A limitation of these prior studies was the use of imaging technology with limited spatial resolution (7,9,13,30), the small sample size (9), and the use of different measures of mobility. For example, Lois et al. (7) used an overall score of parkinsonian signs and did not examine bradykinesia separately from other signs, but the work of Zimmerman (9) and our reports (13,30) examined different gait parameters of step and stride length.

The associations of small vessel disease with bradykinesia and tremor are consistent with previous findings in cohorts of younger old adults without PD (4,6,7). However, in our study, the association of WMHv with bradykinesia was substantially weakened in fully adjusted models. It is possible that focal gray matter atrophy of these regions plays a more important role in regulating motor slowing and gait disturbances compared with total burden of small vessel disease.

Although none of the participants had overt neurological disease impairing mobility, information processing speed or memory/mood domains, worse performance on these tests

Table 3. Association of MRI Measures (independent variable) With the Mobility Measures (dependent variables) of Bradykinesia, Gait Disturbances, and Gait <1.0 m/s

MRI Measures in the Model	Model 1	Model 2: Further Adjusted for Total Brain WMHv	Model 3: Model 2 Further Adjusted for Age	Model 4: Model 3 Further Adjusted for Prevalent Cardiovascular Disease, Stroke, Myocardial Infarction
Outcome: Presence of bradykinesia				
Primary sensorimotor cortex*	0.41 (0.28, 0.60), $p < .0001$	0.43 (0.29, 0.64), $p < .0001$	0.46 (0.31, 0.68), $p < .0001$	0.46 (0.31, 0.68), $p < .0001$
Total brain WMHv	—	1.31 (1.03, 1.74), $p = .03$	1.29 (0.99, 1.68), $p = .06$	1.30 (0.99, 1.71), $p = .06$
Outcome: presence of gait disturbances				
Medial temporal area†	0.55 (0.39, 0.77), $p < .0001$	0.56 (0.40, 0.78), $p < .0001$	0.56 (0.42, 0.83), $p < .0001$	0.58 (0.41, 0.82), $p < .0001$
Total brain WMHv	—	1.10 (0.85, 1.41), $p = .47$	1.04 (0.80, 1.35), $p = .52$	1.05 (0.80, 1.38), $p = .71$

Notes: Each column reports standardized odds ratio adjusted for intracranial volume, 95% confidence intervals, and p value adjusted for intracranial volume of each MRI measure in the model. MRI = magnetic resonance imaging; WMHv = white matter hyperintensities volume.

*Sum of gray matter volume of precentral and postcentral gyri.

†Sum of gray matter volume of hippocampus, parahippocampus, amygdale, and entorhinal cortex.

was associated with prevalence of bradykinesia, gait disturbances, and tremor. This is consistent with prior literature reporting associations of impairment in mood and multiple domains of cognition with parkinsonian signs (10,11,31). These associations suggest that these domains may share overlapping brain resources with bradykinesia, gait disturbances, and tremor. Adjustment for these tests did not attenuate the associations of the sensorimotor area with bradykinesia or the associations of the medial temporal area with gait disturbances. Thus, the potential overlap between these domains might be localized in other brain regions and/or within more complex networks. An analysis of brain networks that accounts for individual white matter tracts in addition to gray matter regions is warranted to answer this question.

The associations of basal ganglia with bradykinesia, gait disturbances, and tremor were all not significant. These negative findings raise the question of whether these signs in community-dwelling older adults are an entity separate from the clinical manifestation of PD. Most neuroimaging studies have examined patients with diagnosis of PD (32–35) and have focused on differential diagnosis with other atypical parkinsonian signs (36). Previous neuroimaging studies of adults without PD have relied on lower resolution methods and have not examined regions of interest (4,6,7). Another explanation for these negative findings is that structural imaging methods alone do not capture the key abnormalities related to early PD pathology. In fact, PD neuroimaging findings are remarkably similar to that of normal controls on conventional structural magnetic resonance imaging (33,35,37,38) with the exception of some borderline differences in voxel-based morphometry of structural and diffusion-weighted imaging (32,35,37) and possibly modest accelerated atrophy rates over time (34,39). More recent applications of cerebral glucose metabolism and resting state connectivity methods have revealed involvement of basal ganglia in PD patients (32,33). An integrated approach of neuroimaging,

neuroepidemiological, and postmortem methodologies in a longitudinal study design can help clarify the pathophysiology underlying bradykinesia and gait disturbances in older adults without PD.

Strengths of this study include the extensive characterization of neuroimaging data and of health-related conditions that can potentially contribute to mobility disturbances above and beyond the neuroimaging markers. The relatively small sample size and low frequency of tremor did not provide power to analyze neuroimaging patterns by co-occurrence of signs. Future studies with larger sample sizes are warranted to address this question and also to address generalizability of the results. Because this cohort was based on volunteer participation, these adults may have been healthier than other community-dwelling adults, 80 years and older. The selection criteria could explain the relatively low percentage of parkinsonian signs relative to some other cohorts of similar age (2).

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SUPPLEMENTARY MATERIAL

Supplementary material can be found at: <http://biomedgerontology.oxfordjournals.org/>

REFERENCES

1. Louis ED, BD. Mild parkinsonian signs: an overview of an emerging concept. *Mov Disord.* 2007;22:1681–1688.
2. Bennett DA, Beckett LA, Murray AM, Shannon KM, Goetz CG, Pilgrim DM, Evans DA. Prevalence of parkinsonian signs and associated mortality in a community population of older people. *N Engl J Med.* 1996;334:71–76.
3. Racette BA GL, Kissel AM, Criswell SR, Perlmuter JS. A population-based study of parkinsonism in an Amish community. *Neuroepidemiology.* 2009;33:225–230.

4. de Laat K, van Norden AG, van Oudheusden LJ, van Uden IW, Norris DG, Zwiers MP, de Leeuw FE. Diffusion tensor imaging and mild parkinsonian signs in cerebral small vessel disease. *Neurobiol Aging*. 2011.
5. Murray AM, Bennett DA, Mendes de Leon CF, Beckett LA, Evans DA. A longitudinal study of parkinsonism and disability in a community population of older people. *J Gerontol A Biol Sci Med Sci*. 2004;59:864–870.
6. Reitz C, Trenkwalder C, Kretschmar K, Roesler A, Eckardstein V, Berger K. Relation of cerebral small-vessel disease and brain atrophy to mild Parkinsonism in the elderly. *Mov Disord*. 2006;21:1914–1919.
7. Louis ED, Brickman AM, DeCarli C, et al. Quantitative brain measurements in community-dwelling elderly persons with mild parkinsonian signs. *Arch Neurol*. 2008;65:1649–1654.
8. Miller WC, DeLong MR. Parkinsonian symptomatology. An anatomical and physiological analysis. *Ann NY Acad Sci*. 1988;515:287–302.
9. Zimmerman ME, Lipton RB, Pan JW, Hetherington HP, Verghese J. MRI- and MRS-derived hippocampal correlates of quantitative locomotor function in older adults. *Brain Res*. 2009;1291:73–81.
10. Lauterbach EC. The neuropsychiatry of Parkinson's disease and related disorders. *Psychiatr Clin North Am*. 2004;27:801–825.
11. Kehagia AA, Barker RA, Robbins TW. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *Lancet Neurol*. 9:1200–1213.
12. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord*. 2008;23:329–342, quiz 472.
13. Rosano C, Aizenstein H, Brach J, Longenberger A, Studenski S, Newman AB. Special article: gait measures indicate underlying focal gray matter atrophy in the brain of older adults. *J Gerontol A Biol Sci Med Sci*. 2008;63:1380–1388.
14. Simonsick EM, Newman AB, Nevitt MC, et al. Measuring higher level physical function in well-functioning older adults: expanding familiar approaches in the Health ABC study. *J Gerontol A Biol Sci Med Sci*. 2001;56:M644–M649.
15. Venkatraman V, Aizenstein HJ, Newman AB, et al. Lower digit symbol substitution score in the oldest old is related to magnetization transfer and diffusion tensor imaging of the white matter. *Frontiers in Neuroscience*. 2011;3:11.
16. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation maximization algorithm. *IEEE Trans Med Imaging*. 2001;20:45–57.
17. Wu M, Rosano C, Butters M, et al. A fully automated method for quantifying and localizing white matter hyperintensities on MR images. *Psychiatry Res*. 2006;148:133–142.
18. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage*. 2006;31:1487–1505.
19. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002;15(1):273–289.
20. Bennett DA, Shannon KM, Beckett LA, Wilson RS. Dimensionality of parkinsonian signs in aging and Alzheimer's disease. *J Gerontol A Biol Sci Med Sci*. 1999;54:M191–M196.
21. Marttila RJ, Rinne UK. Level of blood pressure in patients with Parkinson's disease. A case-control study. *Eur Neurol*. 1977;16:73–78.
22. Knopman DS, Penman AD, Catellier DJ, et al. Vascular risk factors and longitudinal changes on brain MRI: the ARIC study. *Neurology*. 2011;76(22):1879–1885.
23. Newman AB, Kupelian V, Visser M, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *J Gerontol A Biol Sci Med Sci*. 2006;61:72–77.
24. Rosano C, Simonsick EM, Harris T, et al. Association between physical and cognitive function in healthy elderly: the health, aging and body composition study. *Neuroepidemiology*. 2005;24:8–14.
25. Yu H, Sternad D, Corcos DM, Vaillancourt DE. Role of hyperactive cerebellum and motor cortex in Parkinson's disease. *Neuroimage*. 2007;35:222–233.
26. Turner RS, Grafton ST, McIntosh AR, DeLong MR, Hoffman JM. The functional anatomy of parkinsonian bradykinesia. *Neuroimage*. 2003;19:163–179.
27. Markesbery WR. Neuropathologic alterations in mild cognitive impairment: a review. *J Alzheimers Dis*. 2010;19:221–228.
28. Axer H, Axer M, Sauer H, Witte OW, Hagemann G. Falls and gait disorders in geriatric neurology. *Clin Neurol Neurosurg*. 2010;112:265–274.
29. Vanderwolf C. Hippocampal electrical activity and voluntary movement in the rat. *Electroencephalogr Clin Neurophysiol*. 1969;26:407–418.
30. Rosano C, Aizenstein HJ, Studenski S, Newman AB. A regions-of-interest volumetric analysis of mobility limitations in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci*. 2007;62:1048–1055.
31. Kawamura M, Kobayakawa M. Emotional impairment in Parkinson's disease. *Parkinsonism Relat Disord*. 2009;15:S47–S52.
32. Brooks DJ. Imaging approaches to Parkinson disease. *J Nucl Med*. 2010;51(4):596–609.
33. Dalaker TO, Larsen JP, Bergsland N, et al. Brain atrophy and white matter hyperintensities in early Parkinson's disease(a). *Mov Disord*. 2009;24:2233–2241.
34. Burton EJ, McKeith IG, Burn DJ, O'Brien JT. Brain atrophy rates in Parkinson's disease with and without dementia using serial magnetic resonance imaging. *Mov Disord*. 2005;20:1571–1576.
35. Sitburana O, Ondo WG. Brain magnetic resonance imaging (MRI) in parkinsonian disorders. *Parkinsonism Relat Disord*. 2009;15:165–174.
36. Seppi K, Poewe W. Brain magnetic resonance imaging techniques in the diagnosis of parkinsonian syndromes. *Neuroimaging Clin North Am*. 2010;20(1):29–55.
37. Hotter A, Esterhammer R, Schocke MF, Seppi K. Potential of advanced MR imaging techniques in the differential diagnosis of parkinsonism. *Mov Disord*. 2009;24(suppl 2):S711–S720.
38. Vasconcellos LF, Novis SA, Moreira DM, Rosso AL, Leite AC. Neuroimaging in Parkinsonism: a study with magnetic resonance and spectroscopy as tools in the differential diagnosis. *Arq Neuropsiquiatr*. 2009;67:1–6.
39. Wild E, Fox NC. Serial volumetric MRI in parkinsonian disorders. *Mov Disord*. 2009;24:S691–S698.