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Slower gait, slower information processing and smaller prefrontal area in older adults

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Abstract

Background: slower gait in older adults is related to smaller volume of the prefrontal area (PFAv). The pathways underlying this association have not yet been explored. Understanding slowing gait could help improve function in older age. We examine whether the association between smaller PFAv and slower gait is explained by lower performance on numerous neuropsychological tests.
Hypothesis: we hypothesise that slower information processing explains this association, while tests of language or memory will not.
Methods: data on brain imaging, neuropsychological tests (information processing speed, visuospatial attention, memory, language, mood) and time to walk 15 feet were obtained in 214 adults (73.3 years, 62% women) free from stroke and dementia. Covariates included central (white matter hyperintensities, vision) and peripheral contributors of gait (vibration sense, muscle strength, arthritis, body mass index), demographics (age, race, gender, education), as well as markers of prevalent vascular diseases (cardiovascular disease, diabetes and ankle arm index).
Results: in linear regression models, smaller PFAv was associated with slower time to walk independent of covariates. This association was no longer significant after adding information processing speed to the model. None of the other neuropsychological tests significantly attenuated this association.
Conclusions: we conclude that smaller PFAv may contribute to slower gait through slower information processing. Future longitudinal studies are warranted to examine the casual relationship between focal brain atrophy with slowing in information processing and gait.

Keywords: *prefrontal volume, gait speed, information processing, elderly*

Introduction

Slower gait in older adults is an early sign of future cognitive changes [1, 2], it is critical to maintain independence in daily life [3] and it is a powerful predictor of disability and mortality [4–6]. Our recent meta-analysis of nine epidemiological studies indicates that time to walk is a reliable indicator of longevity [5]. Understanding the determinants of slower gait can help understand how to maintain function late in life. There is a general consensus that mobility is regulated by multiple systems, including the central nervous system, peripheral nervous system, musculoskeletal and cardiorespiratory systems. Diseases affecting each of the systems that are involved in mobility control can cause mobility impairment and slowing gait. However, community-dwelling older adults often begin to walk more slowly without an apparent cause or disease [7].

Emerging evidence indicates that brain atrophy is associated with slower gait in community-dwelling older adults [8–10]. Prior work indicates that prefrontal areas are associated with slower gait [8, 9, 11–13]. We have recently shown that there is a selective association between smaller prefrontal area and slower gait in community-dwelling older adults free from dementia and stroke [9, 13]. Prefrontal

areas also regulate information processing speed, which is critical to complete tasks rapidly and efficiently. Therefore, slowing gait could be secondary to prefrontal-related changes in information processing speed. We have previously shown that slower information processing partially explains the association between MRI abnormalities within the entire brain and slowing gait [9, 14]. We propose to extend our prior work and test the hypothesis that slower processing speed explains the association between focal prefrontal volume and time to walk. Specifically, we hypothesise that the association of smaller prefrontal area volume (PFAv) with longer time to walk is explained by lower performance on tests of information processing speed and not on tests of language, memory and mood. Because of the contribution of PFAv to visuospatial attention and the relevance of visuospatial attention to carry out motor tasks, we also hypothesise that the association of PFAv with time to walk is partially explained by performance on visuospatial attention tests. Such information will be critical in designing interventions to improve gait in older adults.

Methods

Study population

The Cardiovascular Health Study (CHS) is a population-based, ongoing study of coronary heart disease and stroke risk in community-dwelling adults 65 years old and older recruited in four clinical centres starting in 1989 (Forsyth County, NC; Sacramento County, CA; Washington County, MD and Pittsburgh, PA). Demographics, information on all hospitalisations, review of medical records, laboratory and clinical evaluations, neurological examination and assessment of health-related factors were characterised [15]. Brain MRIs were acquired in 523 participants in Pittsburgh in 1997–99 [16]. For this study, we re-read a random sample of 235 brain MRIs using an automated technique as described below. The remaining 288/523 participants, whose MRIs had not been re-read, were similar to the 235 participants with regard to demographics or health-related factors (data not shown). Adults with dementia or stroke (n = 21) were identified as detailed previously [16, 17] and excluded from this cohort thus yielding a sample of 214 participants with complete data on brain volumes, cognitive tests and gait speed.

Brain measurements

Images were collected in 1997–99 at the University of Pittsburgh Medical Center MR Research Center [18] using a 1.5 T Signa scanner (GE Medical Systems, University of Pittsburgh, Pittsburgh, PA, USA) with high performance gradients (4 G/cm and 150 T/ms) [19]. Three-dimensional Spoiled Gradient Recalled and scout T1-weighted images were obtained, followed by standardised sagittal T1-weighted spin-echo images, spin density/T2-weighted and axial T1-weighted images.

Brain volumes were obtained using a procedure previously described [20–23]. Regions of interest, including all Brodmann areas and subcortical structures, were drawn on a template brain using the automated anatomical labelling neuroanatomical atlas [21, 24]. After skull and scalp stripping [25], and segmentation of grey matter, white matter and cerebrospinal fluid, the brain atlas and the brain of the individual are aligned. Intensity normalisation is done on each individual's image as well as on the colin27 template to give each individual the same orientation and image-intensity distribution as the template and to improve the registration accuracy. A fully deformable automatic algorithm minimised measurement inaccuracies while allowing for a high degree of spatial deformation.

Grey matter volume was calculated for the all brain as the sum of voxel counts from the grey matter, the white matter, and the cerebrospinal fluid. Grey matter volume of the PFAv was computed as the number of voxels contained within the middle frontal gyrus. White matter hyperintensities were visually rated by study radiologists on a 10-point scale from 0 to 9 (worst) [18] and coded as severe if grade was ≥3 and low if grade was <3 [26]. The largest right–left diameter from the inner table of the skull was computed (in centimetre) on the brain MRI and was used as a measure of head size.

Mobility measures

The participants of this study were all able to walk. Time to walk a 15-foot course at usual pace from a stand-still position was measured with a stop watch during two trials. The average of the two trials was computed and used as the variable of interest.

Neuropsychological assessment

Details on the battery of neuropsychiatric tests have been previously published [27]. Tests of information processing speed included the Digit Symbol Substitution Test (DSST), the Stroop Neuropsychological Screening Test and the Trails Making Test (computed as score on trails B/score on trails A). Tests requiring visuospatial and perceptual attention were: the Raven's Coloured Progressive Matrices and the Rey–Osterreith figure copy. Tests of memory included the Immediate and delayed recall of the Rey–Osterreith figure, and the California Verbal Learning Test. Data on global function [Teng Modified Mini-Mental State Examination (MMSE)], mood (Center for Epidemiologic Studies Depression Scale) and motor dexterity (finger tap) were also obtained [26, 27].

Other contributors to time to walk

In addition to demographics (age, gender and education), head size was included in all models because larger heads are associated with overall larger brain volumes. Known contributors of slower gait including visual acuity, body

mass index, self-reported hip/knee pain, arthritis, vibratory sensory impairment, muscle strength and markers of vascular-related conditions were assessed and investigated as significant co-factors in step-wise regressions [28–30]. Vibratory sensation was measured by placing a tuning fork at the toes, and the ability to perceive the vibration of the tuning fork at the toe was rated over two trials. If no vibration was perceived at the toes, then the tuning fork was placed at the malleoli and vibration perception was rated over two trials. Vibratory impairment was rated from 0 (no impairment perceiving tuning fork at the toes, either right or left) to 5 (bilateral impairment at both ankles). Grip strength was measured as the average strength in kilograms from two handheld dynamometer trials from the dominant hand. We also controlled for markers of vascular-related conditions, including ankle–arm index >0.9, a measure of peripheral arterial disease, diabetes and prevalent cardiovascular diseases [10, 31]. The mean (standard deviation) interval of time between MRI, gait and cognitive tests was of 2.5 (3.6) months and it was added to the model as a covariate.

Statistical analysis

In this cross-sectional analysis, standardised coefficients (e.g. estimated change in the dependent variable for each standard deviation of the independent variable) were reported for all regression models. Standardisation of the coefficients was done to compare the relationships between each of the independent variables with the depended variable while addressing the fact that the independent variables were measured in different units of measurement. Measures were inspected for normality and log transformed if the skewness index was more than two times greater than its SD.

Forward stepwise regression models were used to test that the association of PFAv (independent variable) with time to walk (dependent variable) remained independent of covariates while addressing potential collinearity between covariates. At each step, the independent variable not in the equation that had the smallest probability of F was entered, if that probability was sufficiently small ($P < 0.05$). Variables already in the regression equation were removed if their probability of F became sufficiently large ($P > 0.1$). The method terminated when no more variables were eligible for inclusion or removal.

Age-adjusted regression models were used to estimate the association of the cognitive tests' scores with PFAv and time to walk. The cognitive tests that were significantly and independently associated with both PFAv and time to walk were considered as *candidate explanatory factors* and entered a regression model built with time to walk (dependent variable) and PFAv (independent variable). We defined as *explanatory factors* those cognitive tests that *produced* a change in the regression coefficient of PFAv that was >10% [32] and significantly different from 0 [33], according to the Barron model and the Sobel test and non-parametric bootstrapping, respectively. All analyses were repeated after adjustment for total brain volume and head size and for time between MRI and tests' measurements. SPSS for Windows (version 17.0; SPSS, Inc., Chicago, IL, USA) was used for all analyses.

Results

The study population was a diverse group of older adults (Table 1), with a high-school or higher level of education and with gait and cognitive scores in the normal range [26].

In the last step of the forward stepwise model of PFAv predicting time to walk, only PFAv, muscle strength and

Table 1. Prevalence and mean values of variables of interest in the study population ($n = 214$)

	Mean values (standard deviations) or number (%)
Demographics	
Age, year	72.82 (3.77)
Race, white	164 (76.6)
Gender, female	138 (64.5)
Education, years	14.07 (2.44)
Dependent variable, unit	
Time to walk 1 m, s	1.13 (0.30)[a]
Independent variables	
Grey matter of the prefrontal area, cubic millimeters	23.41 (3.32)
Neuropsychological tests	
Information processing speed	
Digit symbol substitution test	45.04 (12.55)
Trail B/A	2.14 (1.70)
Stroop	57.89 (35.65)
Visuospatial and perceptual attention	
Raven's Coloured Progressive Matrices	25.93 (7.73)
Rey–Osterreith figure copy	20.51 (5.84)
Memory	
Rey–Osterreith figure delayed recall	12.19 (6.31)
California Verbal Language Test	7.59 (3.67)
Language	
Word generation (letters)	23.70 (10.64)
Mood	
Center for Epidemiologic Studies Depression	5.51 (4.60)
Scale	
Global function	
Modified Mini-Mental State Examination	94.84 (5.56)
Other tests	
Finger tap (number/15 s)	59.48 (10.33)
Other central contributors of slowing gait	
White matter hyperintensities ≥grade 3, presence	71 (33)
Intracranial volume, cubic millimeters	133.5 (13.4)
Vision problems, presence	25 (14.9)
Peripheral contributors of slowing gait	
Muscle strength (kg)[b]	27.49 (9.26)
Arthritis at either knee/hip, presence	60 (28.0)
Impaired vibration sensitivity at either toe, presence	133 (50.7)
Markers of vascular-related conditions	
Diabetes, presence	32 (15.0)
Ankle–arm index ≥0.9, presence	138 (64.5)
Prevalent cardiovascular disease, presence of any	54 (25.2)
Body mass index, kg/h^2	25.81 (3.59)

[a]This value corresponds to an average (SD) speed of walking of 0.94 (0.2) m/s.
[b]Average strength from dominant hand.

Table 2. Association of neuropsychological tests with prefrontal area volume and time to walk

Domain	Test name	Age-adjusted standardised regression coefficients[b] and *P*-value	
		Time to walk 1 m	Prefrontal area volume
Information processing speed	Digit symbol substitution test[a]	−0.18, $P = 0.01$	0.28, $P \leq 0.0001$
	Trail B/A	0.02, $P = 0.8$	0.008, $P = 0.9$
	Stroop	−0.15, $P = 0.02$	0.09, $P = 0.2$
Visuospatial and perceptual attention	Raven's Coloured Progressive Matrices[a]	−0.16, $P = 0.02$	0.15, $P = 0.03$
	Rey–Osterreith figure copy	−0.16, $P = 0.02$	0.06, $P = 0.4$
Memory	Rey–Osterreith figure delayed recall[a]	−0.15, $P = 0.03$	−0.16, $P = 0.02$
	California Verbal Language Test	−0.11, $P = 0.1$	0.08, $P = 0.2$
Language	Word generation (letters)	−0.16, $P = 0.02$	0.06, $P = 0.4$
Other brain function tests			
Mood	CES-D	0.12, $P = 0.08$	0.11, $P = 0.09$
Global function	Modified Mini-Mental score	−0.10, $P = 0.2$	−0.10, $P = 0.1$
Other tests	Finger tap[a]	−0.22, $P = 0.001$	0.15, $P = 0.03$

[a]Difference in time to walk or in PFAv for one SD of cognitive test score.
[b]Tests that are significantly associated with PFAv and also with time to walk at $P < 0.05$ and are considered as candidate explanatory factors.

arthritis remained independently associated with time to walk [standardised beta (*P*-value): −0.15 ($P = 0.02$), −0.26 ($P < 0.0001$) and 0.23 ($P < 0.0001$), respectively].

In age-adjusted linear regression models (Table 2), one of the three measures of psychomotor processing speed (DSST), one of the two tests of visuospatial/perceptual attention (Raven's matrices), one of the two tests of memory (Rey–Osterreith Figure Delayed Recall) and the finger tap test were each significantly associated with both PFAv and time to walk. Associations with time to walk were all in the expected direction and effect size were remarkably similar across tests. For example, for each standard deviation of any of the tests' score, there was a difference in time to walk of 0.15–0.18 s (approximately 0.17/0.14 m/s). Associations with PFAv were also in the expected direction, and were stronger for DSST than for the Raven's matrices, Rey–Osterreith Figure Delayed Recall, and finger tap test. One SD of DSST score was associated with a PFAv difference of 0.28 mm^3. Only these four measures (DSST, Raven's matrices, Rey figure copy, finger tap) were considered as candidate explanatory factors of the association between PFAv and time to walk in further analyses. Measures that were associated only with time to walk or with PFAv or with neither were not considered in further analyses. Analyses with variables that were not normally distributed (Stroop, Raven's coloured matrices test, MMSE score and depression score) were repeated after log transformation of these variables. Results were similar (not shown) and are reported for the untransformed variables.

The DSST, Raven's matrices, Rey figure copy and finger tap each changed the regression coefficient of PFAv predicting time to walk by more than 10% (Table 3). However, attenuation was stronger for DSST compared with other tests (32% change) and the size of the attenuation was significantly different from 0 for DSST but not for Raven's matrices, Rey figure copy or finger tap. The effect of DSST on the association of PFAv with time to walk was not substantially modified by covariates, including age, or by total brain volume or by total grey matter or by white matter hyperintensities ≥grade 3 (not shown).

Discussion

In this cohort of older adults free from stroke and dementia, the association of smaller PFAv with slower gait is explained by lower performance in one selected cognitive domain, that is slower information processing. Moreover, among the tests of information processing speed, DSST was the only test to be associated with both PFAv and time to walk, and the only test that explained the association of PFAv with time to walk.

Performing the DSST may require skills that overlap with the skills required to walk. For example, performing the DSST requires the ability to interpret geometrical symbols, unlike the Stroop and Trail tests. This specific aspect of DSST might be related to time to walk, because walking requires perception and interpretation of terrain's properties and obstacles in the surrounding space. Although performing the DSST and walking also share time-dependent aspects, these might be less important. In fact, other timed tests examined here (TRAILS B/A, Stroop and finger tap) did not explain the association of PFAv with time to walk. The finger tap, which requires motor dexterity and is a timed task, had a nearly significant effect on the association between PFAv and time to walk and it explained a slightly larger portion of the variance of time to walk when compared with the DSST.

Using markers of overall brain abnormalities, we had previously shown that DSST attenuated the association of brain MRI abnormalities with slowing gait [9, 14]. This work advances our prior knowledge of the interrelationship between brain and gait, because it examines grey matter volume of a specific region of interest with respect to numerous neuropsychological tests beyond the DSST.

Contrary to our hypothesis, performance on tests of visuospatial attention, and specifically the Raven's Coloured Progressive Matrices, did not significantly attenuate the association of PFAv with time to walk, although this test was associated with both PFAv and time to walk. It is possible that these negative findings might be attributed to the fact that our analyses focused on the prefrontal lobe. Another negative finding was the lack of association with memory, language, general function or mood. We had expected this

Table 3. Results of non-parametric bootstrapping test of indirect effect to test mediators of the association between prefrontal area volume (PFAv, independent variable, X) and time to walk in seconds (dependent variable, Y)

	Standardised β coefficient (standard error), *P*–value	Change of β coefficient, mean (95% confidence interval)[b]	Change of β coefficient, %	Bootstrap test of indirect effect
Total effect of X (PFAv) on Y (time to walk)	−0.15 (0.06) $P = 0.02$	n/a	n/a	n/a
Test for candidate explanatory factors[a]				
Effect of X on Y after adjusting for DSST	−0.10 (0.07) $P = 0.1$	−0.05 (−0.10, −0.005)	32	*P = 0.04*
Effect of X on Y after adjusting for Raven's matrices	−0.13 (0.06) $P = 0.06$	−0.02 (−0.05, 0.001)	16	$P = 0.1$
Effect of X on Y after adjusting for Rey–Osterreith delayed recall	−0.13 (0.06) $P = 0.06$	−0.02 (−0.06, 0.002)	16	*P = 0.1*
Effect of X on Y after adjusting for finger tap	−0.12 (0.06) $P = 0.08$	−0.03 (−0.08, −0.002)	21	$P = 0.06$

Each row reports results from separate models.

[a]Tests scores that were significantly ($P < 0.05$) associated with both the dependent variable (time to walk) and the independent variable (prefrontal area) (see Table 2).

[b]The change of β coefficient is computed as β coefficient of X predicting Y minus the β coefficient of X predicting Y after adjusting for the potential mediator; the confidence intervals are from the bootstrap test of indirect effect.

finding because these cognitive domains are associated with networks beyond the dorsolateral prefrontal cortex. For example, visuospatial attention relies on integrity of posterior parietal regions, basal ganglia and the superior longitudinal fasciculus, which connects fronto-parietal regions. Studies of brain networks important for mobility control should also include the anterior corpus callosum, because it connects frontal regions across hemispheres, and the medial temporal lobe and the cingulum (major fibre tract connecting the hippocampus to the frontal lobe), because of their relevance for spatial navigation [34]. Future analyses with larger networks of brain regions and connecting tracts are warranted. Studies with larger sample sizes can also clarify whether the negative findings of this study were due to the lack of statistical power.

These results help our understanding of the determinants of slowed performance in older adults. As PFAv becomes smaller, an overall slowing in processing may result that could affect both information processing (e.g. worsening DSST score) and mobility (slowing gait). Changes in the PFAv may impair cognition (slowed information processing) and slow gait concurrently, or one may appear before the other, depending on a number of other factors. For example, functionality declines of the systems involved in mobility, such as the musculoskeletal and peripheral nervous systems, may accelerate the manifestation and possibly the severity of slowing gait. This study had a cross-sectional design, thus we cannot exclude that there may be other directions of association between PFAv, information processing and time to walk. Although we could not test these hypotheses directly in this cross-sectional study, there is not a clear biological rationale to hypothesise that PFAv would control information processing via gait speed or that information processing speed controls gait through smaller PFAv. Thus, we conclude that the association is most likely to operate in the direction we have proposed. Another limitation of this study was the use of a very crude measure of gait, which is time to walk over a 15-feet walkway. However, this test is a sensitive measure of performance in community-dwelling older adults when compared with other performance measures [3] and it is predictive of more rapid mobility decline over time [6]. Our recent study has shown that this is a reliable measure of survival [5]. Gait speed is a very simple test that can be of clinical utility in geriatric medicine and it is currently the single test being considered by FDA as an outcome measure for clinical trials in older adults [35].

Evidence from prior studies, including our recent functional MRI investigation [36], indicate that PFAv and information processing speed are modifiable late in life. Therefore, future longitudinal studies exploring these cross-over benefits should include a comprehensive brain network analyses and measures of peripheral contributors of gait.

Key points

- The association of PFAv with time to walk is explained by performance on tests of information processing speed.
- The association of PFAv with time to walk is not explained by performance on tests of language, memory, mood.
- The prefrontal area may represent a shared resource for enabling speed both in the cognitive and motor domain.

Conflicts of interest

None declared.

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The impact of dementia on influenza vaccination uptake in community and care home residents

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Abstract

Background: influenza vaccination is recommended for older people irrespective of cognitive decline or residential setting.
Objective: to examine the effect of dementia diagnosis on flu vaccination uptake in community and care home residents in England and Wales.
Methods: retrospective analysis of a primary care database with 378,462 community and 9,106 care (nursing and residential) home residents aged 65–104 in 2008–09. Predictors of vaccine uptake were examined adjusted for age, sex, area deprivation and major chronic diseases.
Results: age and sex standardised uptake of influenza vaccine was 74.7% (95% CI: 73.7–75.8%) in community patients without dementia, 71.4% (69.3–73.5%) in community patients with dementia, 80.5% (78.9–82.2%) in care home patients without dementia and 83.3% (81.4–85.3%) in care home patients with dementia. In a fully adjusted model, compared with community patients without dementia, patients with dementia in the community were less likely to receive vaccination (RR: 0.96, 95% CI: 0.94–0.97) while care home patients with (RR: 1.06, 1.03–1.09) and without (RR: 1.03, 1.01–1.05) dementia were more likely to receive vaccination. Area deprivation and chronic diseases were, respectively, negative and positive predictors of uptake.
Conclusion: lower influenza vaccine uptake among community patients with dementia, compared with care home residents, suggests organisational barriers to community uptake but high uptake among patients with dementia in care homes does not suggest concern over informed consent acts as a barrier. Primary care for community patients with dementia needs to ensure that they receive all appropriate preventive interventions.

Keywords: *influenza vaccination, dementia, nursing homes, ageing*

Introduction

In most developed countries, influenza vaccination is recommended for all older people irrespective of co-morbidity or risk [1]. In the UK, a policy of offering influenza vaccination to all older people over 75 was implemented in 1998 followed by extension to all patients aged 65 and over from 2000 [2]. Vaccination is delivered by general