Mobility and Cognition

Stephanie Studenski MD MPH
Longitudinal Studies Section
Translational Gerontology Branch
Intramural Research Program
National Institute on Aging

Agenda

- Significance
- Key Concepts
- Slowing: a universal clinical indicator
- Preclinical indicators:
  - ➢ variability
  - ➢ loss of reserve (multi-tasking)
  - ➢ altered motor learning
- Mechanisms

Win Animated GIF

An Unrecognized Clinical Reality

An 86 year old man is brought to clinic by his son for a several year history of decline. He has withdrawn from life and spends all his time sitting in a chair dozing. He has had several recent falls.

PMH diabetes on oral agent, HBP

Meds HCTZ, glipizide

Exam shows deficits in cognition specifically construction, sequencing, recall and language. He has a slow shuffling gait and increased tone. His affect is flat and he states that life is not worth living.

He is diagnosed with dementia and depression and given a cane.

Brain-related gait abnormalities in older people are often ignored or attributed to "normal aging".

"senile gait"

An unexplained and disabling problem

"My legs don't move when my brain tells them to. It's very frustrating"

GHW Bush

Does the CNS play a role in this woman's walking?

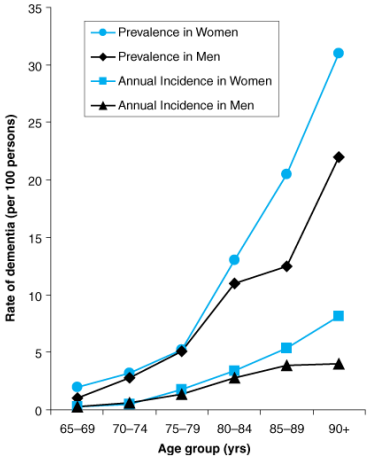
Aging doesn’t have to mean slow walking

Population Impact

The ability to think and to move are essential for independent living. Loss of either or both lead to disability and dependence. Disorders of cognition and movement are common and often coexist in older people

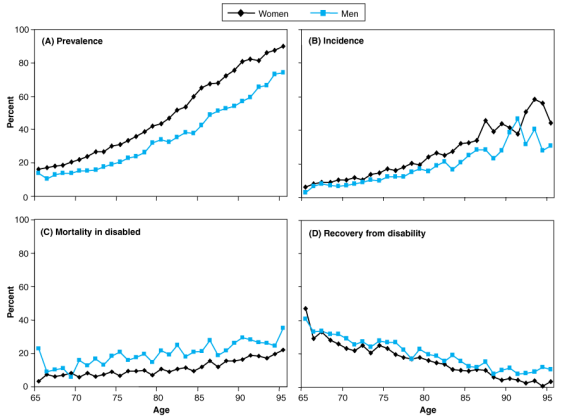
Cognitive Impairment

- Prevalence age 75: 5% M and F
- Prevalence age 85: 12% M 20% F
- Major contributor to disability, need for caregiver, long term care



Mobility Impairment

- Prevalence age 75 20% M 30% F
- Prevalence age 85 40% M 60% F
- Major contributor to disability, need for caregiver, long term care



Guralnik and Ferrucci Epidemiology of Aging in Hazzard text 6th Ed

Thinking and Moving must be studied together

- Extensive epidemiological evidence supports interrelationships between cognition and movement
- Brain networks for movement overlap with networks for cognition
- Thinking and Moving share behavioral and etiological factors that can drive new insights into prevention and treatment

Epidemiology: Gait speed predicts decline in cognitive function

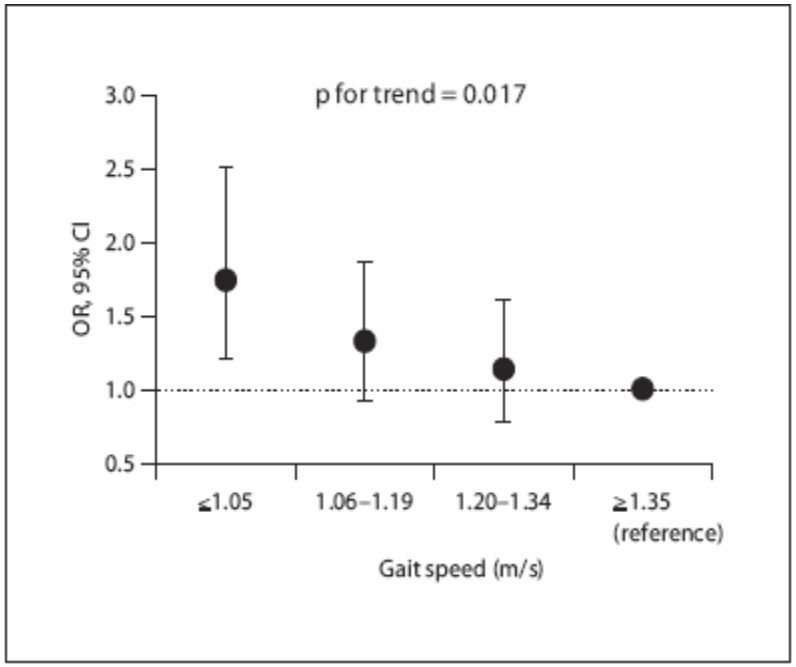


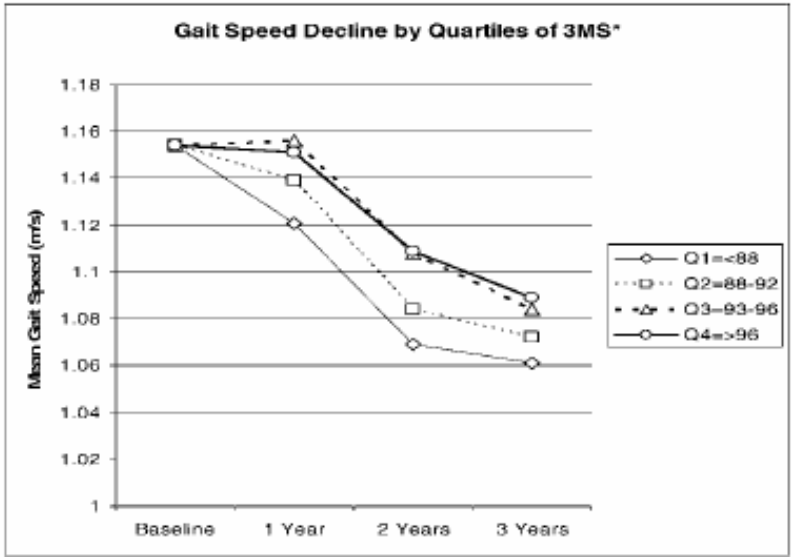
Fig. 2. Risk of decline in DSST [>1 SD (9 points) from mean change] over 5 years, across quartiles of usual gait speed (m/s). Logistic regression model, adjusted for age, gender, race, education, weight, physical activity, cardiovascular comorbidity, high blood pressure, diabetes, chronic obstructive/restrictive pulmonary disease, depressive symptoms, baseline DSST, baseline 3MS, and change in 3MS over time.

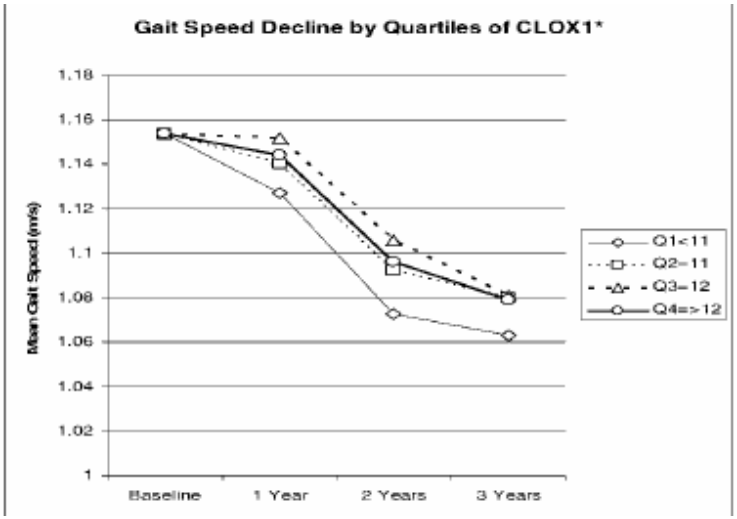
Inzitari et al
Neuroepidemiology 2007

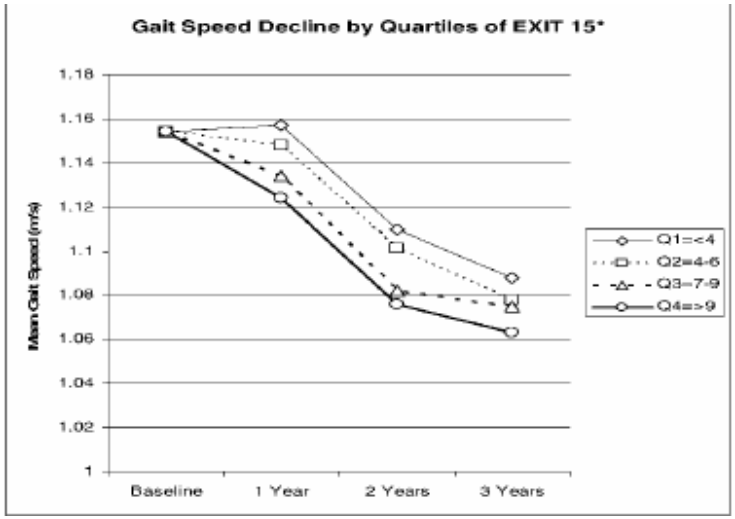
Many others starting in 2002 with Verghese NEJM

Epidemiology: Baseline cognition predicts 3 year change in gait speed

Health ABC Atkinson 2010







The Alzheimers Association discovers walking predicts dementia

Ryan Jaslow CBS News July 16, 2012, 10:35 AM

Slowed walking speed may be early predictor of Alzheimer's decline

(CBS News) New research suggests how a person walks may predict whether they'll develop Alzheimer's disease, a degenerative, incurable brain disease that affects 5.4 million Americans.

Four new studies presented at the Alzheimer's Association International Conference in Vancouver, Canada, tied walking ability to memory and cognitive decline, and may one day help doctors diagnose the disease earlier, researchers say.

Age and Ageing 2012; 41: 58–64
doi: 10.1093/ageing/afr113
Published electronically 28 September 2011

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

Caterina Rosano[1], Stephanie A. Studenski[2], Howard J. Aizenstein[3], Robert M. Boudreau[1], William T. Longstreth Jr[4,5], Anne B. Newman[1]

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.

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, $P\leq0.0001$
	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.

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)

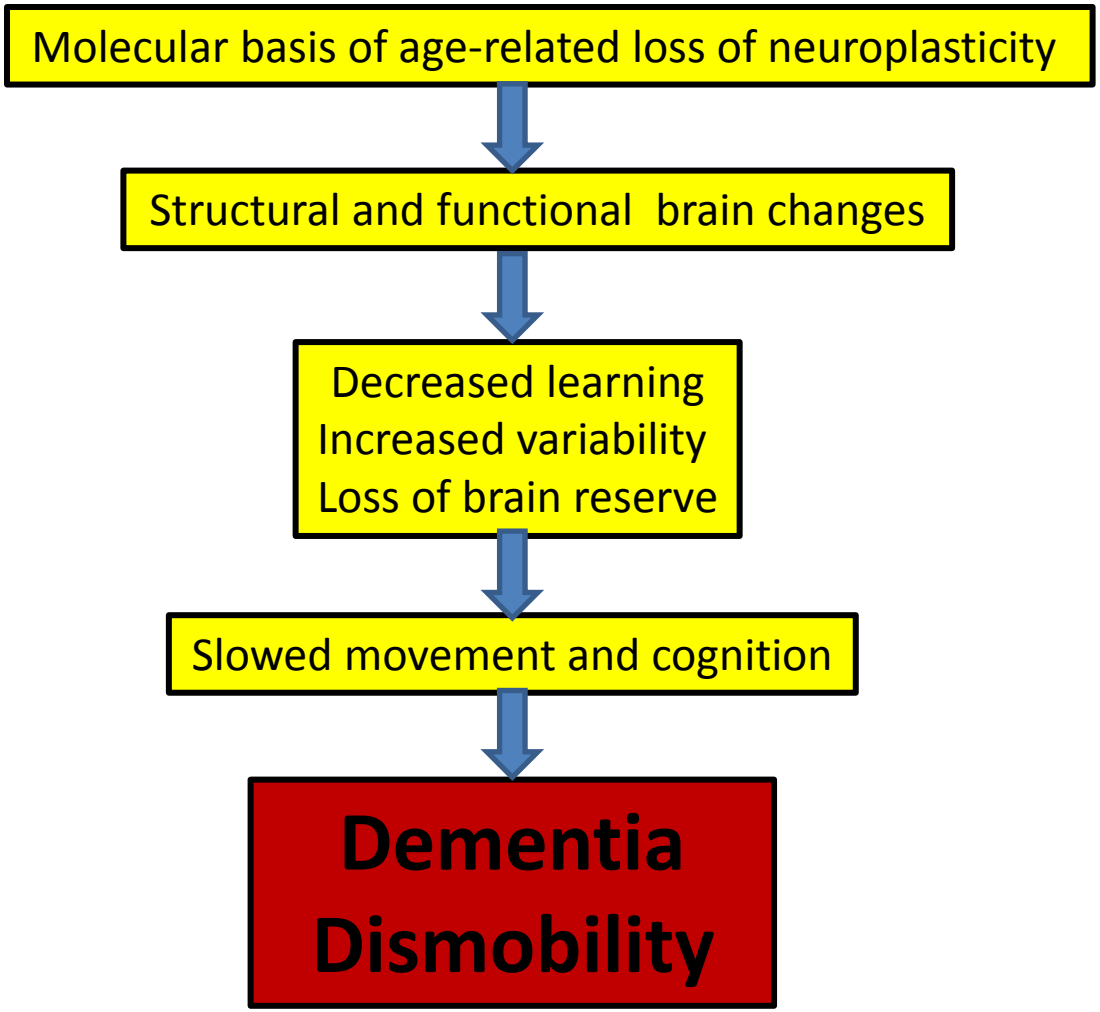
	Standardised β coefficient (standard error), *P*-value	Change of β coefficient, mean (95% confidence interval)[b]	Change of β coefficient, %	Bootstrap test of indirect effect
Total effect of X (PFAv) on Y (time to walk)	−0.15 (0.06) $P=0.02$	n/a	n/a	n/a
Test for candidate explanatory factors[a]				
Effect 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.

The effect of reduced prefrontal brain area on slow gait is mediated by information processing speed

M Albert (personal communication): *DSST is the strongest predictor of future dementia in their cohort*

A model of lifespan effects on motor control



Motor Skill

a link between gait and cognition

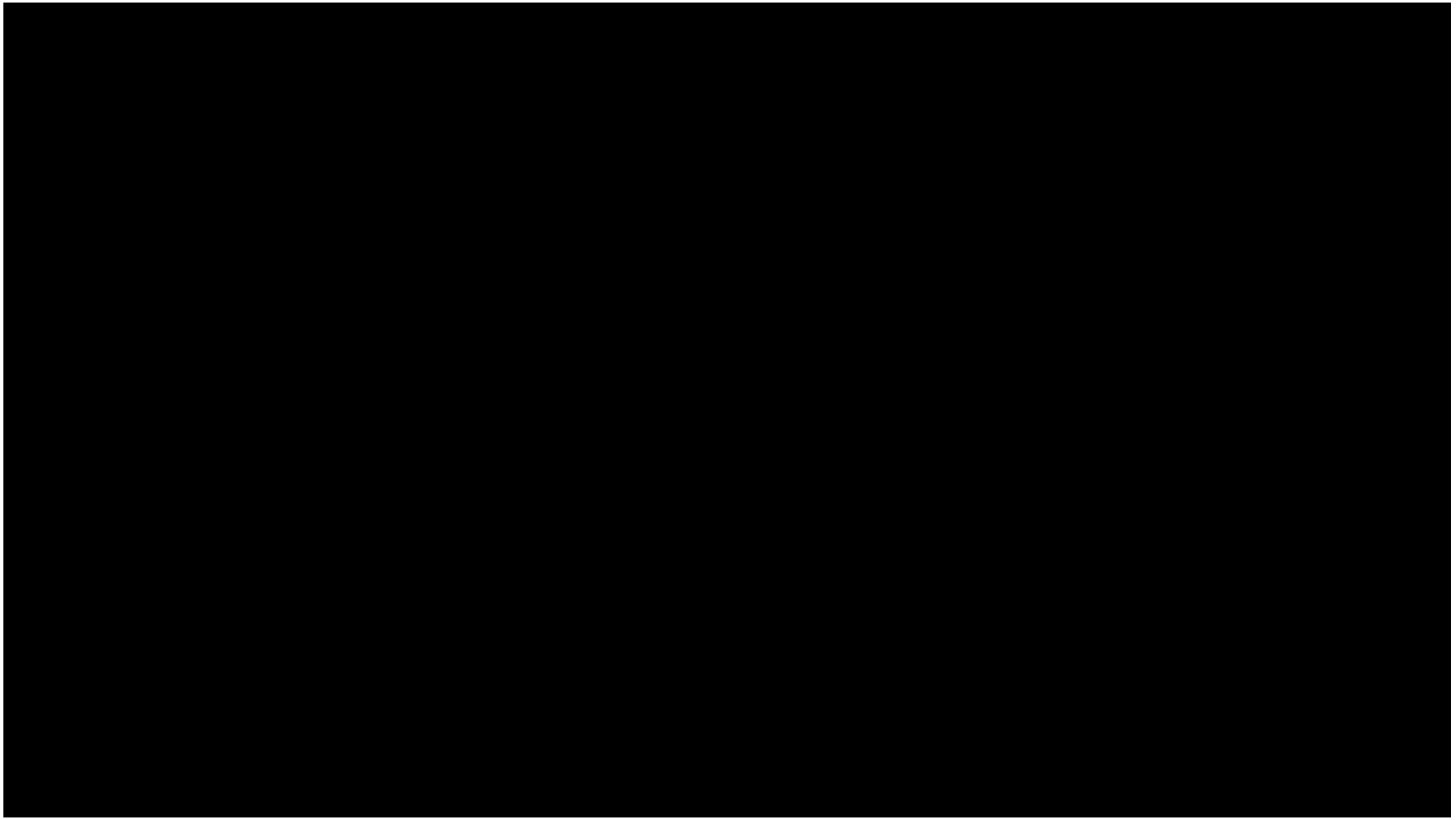
What is Motor Skill?

Smooth efficient learned movement created through motor maps

Characteristics of Novice and Skilled Motor Actions	
Novice movement	**Skilled movement**
Behavioral and Peripheral factors	
○ guided, discontinuous movement, irregular velocity profile ○ task-oriented practice necessary for acquisition of motor sequence learning ○ multiple muscles often activated in a cocontraction pattern ○ movement sequence variable ○ submovements, with stops and starts redirecting path to movement target	○ non-guided, continuous movement, smooth velocity profile ○ practice necessary to achieve and maintain motor expertise (automaticity) ○ multiple muscles activated sequentially in brief bursts ○ preplanned motor sequence ○ movement acceleration and deceleration programmed together
Central factors	
○ brain activity in fronto-parietal [cortico-cortico] pattern of connections ○ sustained, generalized pattern of brain activity ○ cingulate motor area activity high	○ brain activity in cortico-basal ganglia, cortico-cerebellar circuits ○ brief, specific 'efficient' pattern of brain activity ○ reduced cingulate motor area activity

Vanswearingen and Studenski JGMS 2014

Walking is a learned motor skill



Motor Learning: theory of neuroplasticity and long term potentiation

Review Article

Cortical Plasticity during Motor Learning and Recovery after Ischemic Stroke

Jonas A. Hosp[1, 2] and Andreas R. Luft[1, 2, 3]

[1] *Clinical Neurorehabilitation, Department of Neurology, University of Zurich, 8091 Zurich, Switzerland*
[2] *Rehabilitation Institute and Technology Center (RITZ), 8008 Zurich, Switzerland*
[3] *Division of Brain Injury Outcomes, Department of Neurology, Johns Hopkins University, Baltimore, MD 21231, USA*

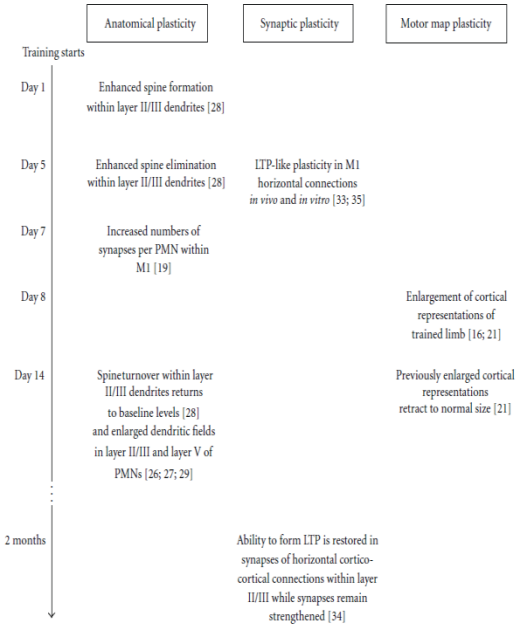
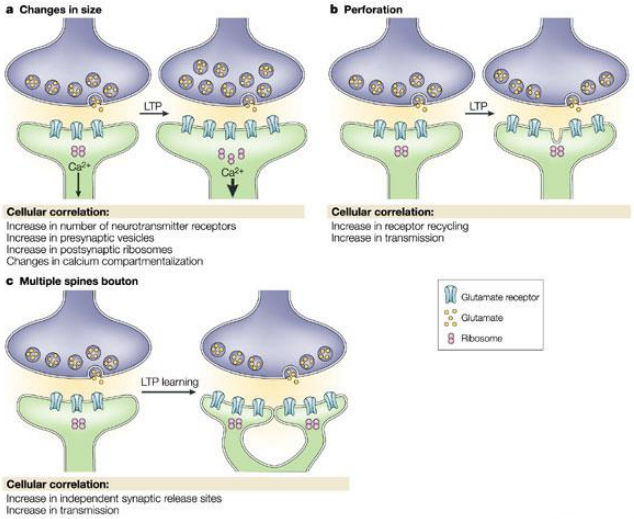
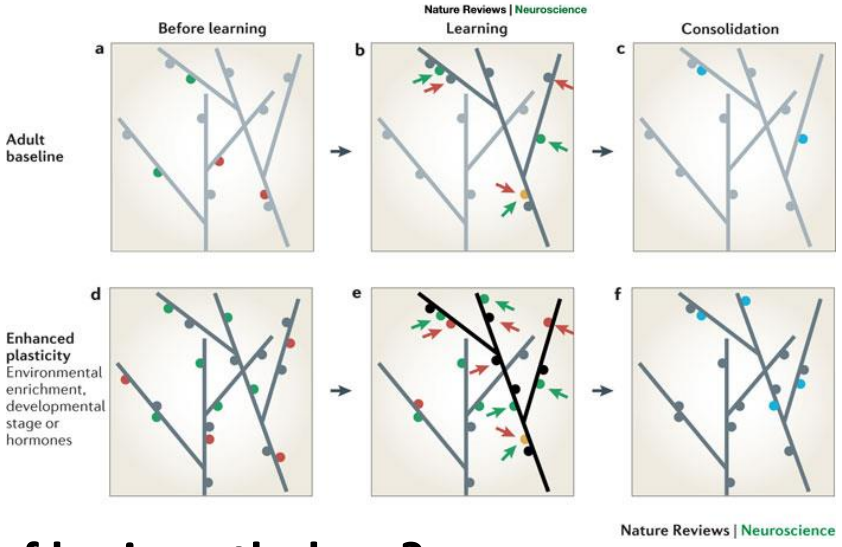


FIGURE 1: Schematic timescale of plasticity in M1 of rodents at different levels induced by a skilled reaching task. PMN: pyramidal motor neuron; LTP: long-term plasticity.





Effect of aging?

Response in the setting of brain pathology?

Signs of Loss of Motor Skill

OVERT

- **Generalized Slowing**
  - motor function
  - psychomotor function

SUBCLINICAL

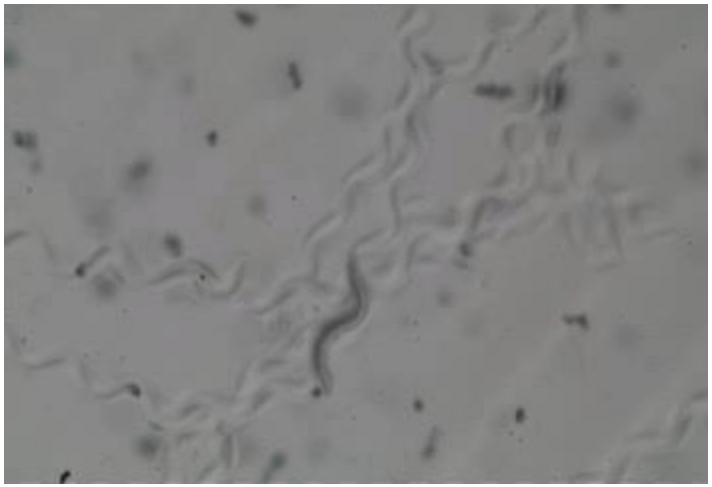
- **Inefficient**
  - Increased energy cost
  - Variable

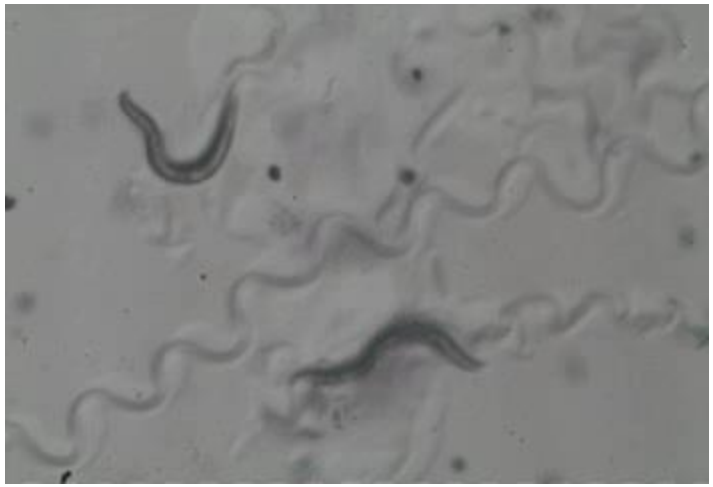
- **Reduced reserve**
  - Dual task cost

- **Reduced plasticity**
  - Slow and incomplete motor learning

SLOWING IS A MAJOR INDICATOR OF HEATLH IN AGING

Movement slows with age

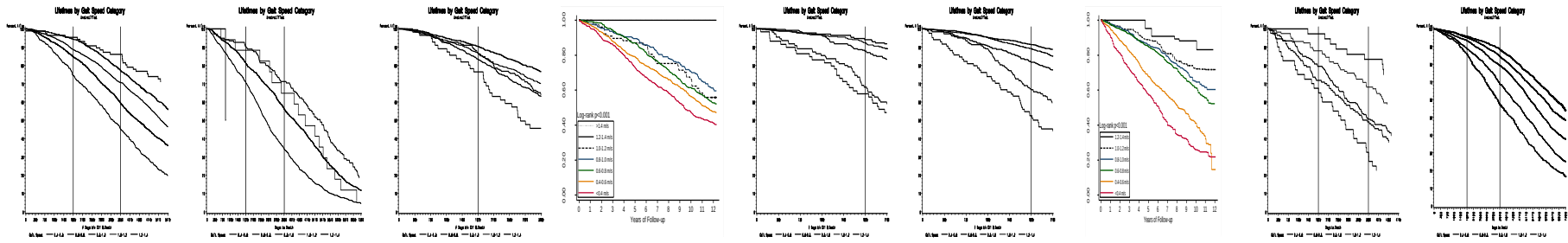




Gait Speed and Survival

Consortium analysis of over 34,000 older adults followed for up to 21 years

	CHS	EPESE	Health ABC	HEPESE	In Chianti	MrOS	NHANES	PEP	SOF
n	5801	2128	3048	1905	972	5833	3958	491	10350
Yrs	16	21	10	12	8	8	12	12	21



JAMA Jan 5, 2011

Gait speed and Survival

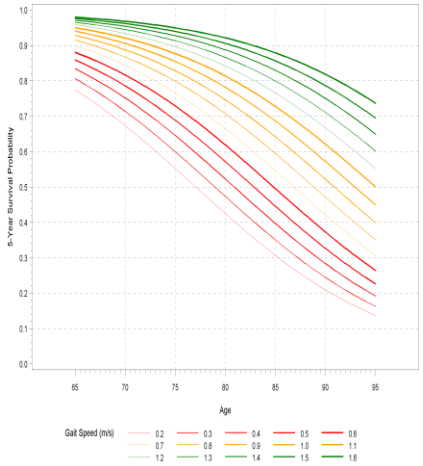
men

NOMOGRAMS

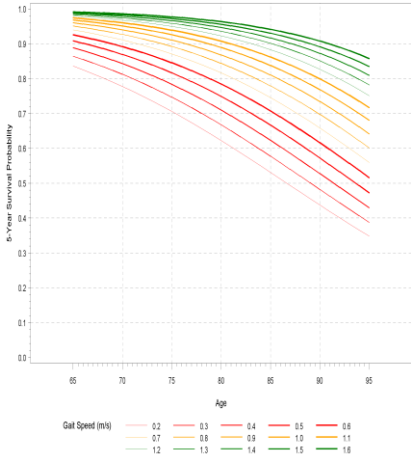
women

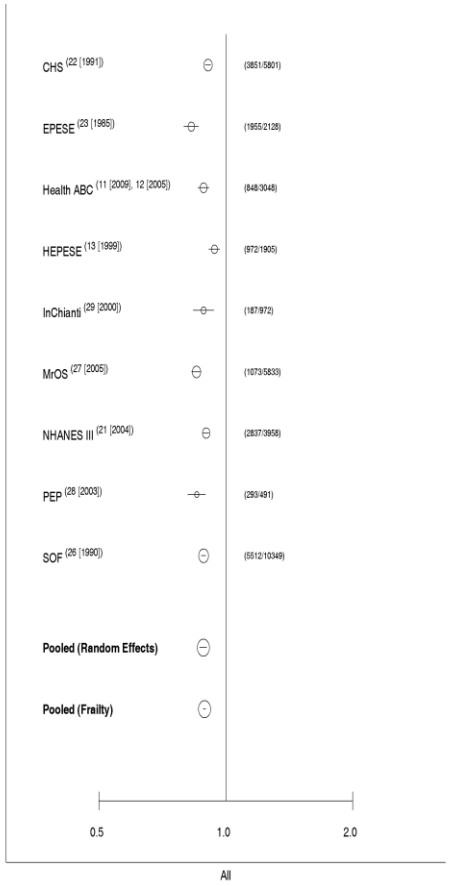
FOREST PLOT

% alive at 5 years

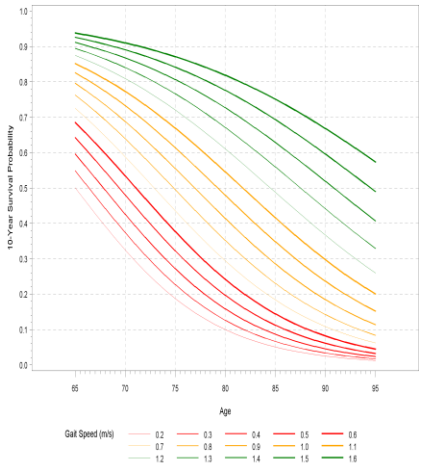


Median survival for age and gender at about 0.8 m/sec

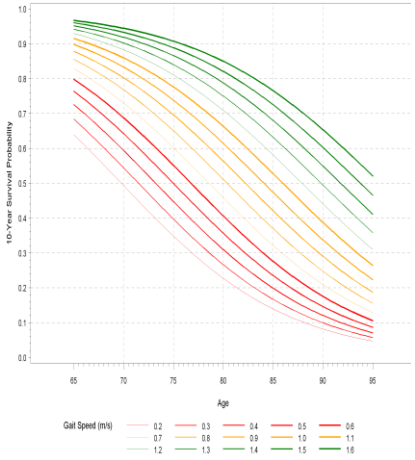




% alive at 10 years



Speeds of 1.0 m/sec or higher suggest healthy aging



JAMA Jan 5, 2011

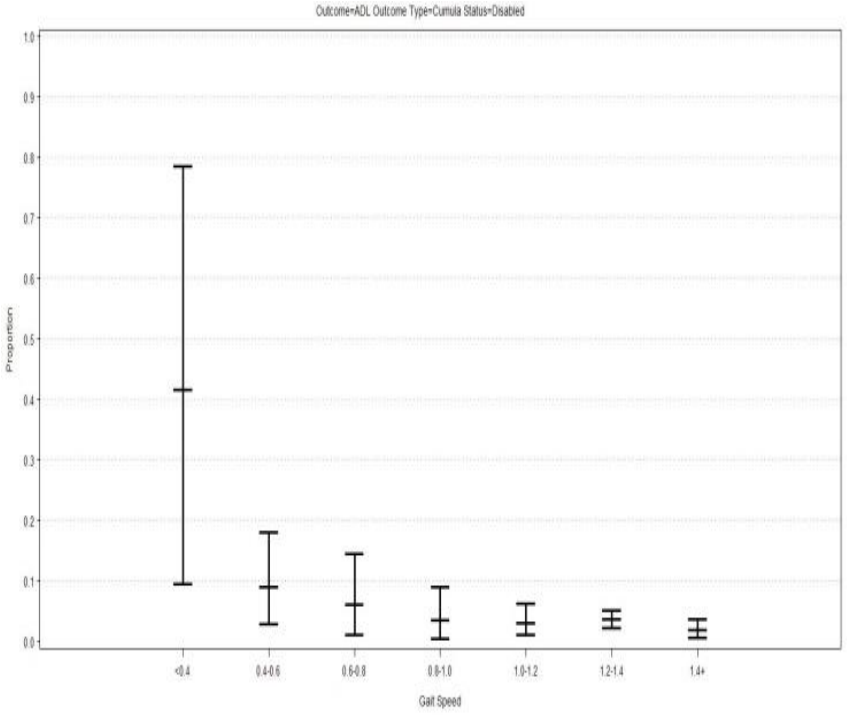
Gait Speed and Disability

Gait Speed as a screen for current disability

Gait speed	Male		Female	
	Se	Sp	Se	Sp
0.5 m/s	.37	.95	.53	.93
0.6	.49	.91	.62	.87
0.7	.60	.85	.73	.78
0.8	.81	.75	.79	.65
0.9	.91	.63	.87	.51
1.0	.94	.45	.92	.31

Cstatistic	0.832	0.807
N	163/4042	474/11416
Mean GS	0.977	0.868

Gait Speed and incident disability over 3 years



Gait Speed and risk of cardiac surgery

J Am Coll Cardiol. 2010 Nov 9;56(20):1668-76.

Cardiac Surgery

Gait Speed as an Incremental Predictor of Mortality and Major Morbidity in Elderly Patients Undergoing Cardiac Surgery

Jonathan Afilalo, MD, MSc,*† Mark J. Eisenberg, MD, MPH,*‡ Jean-François Morin, MD,§ Howard Bergman, MD,‡‖¶ Johanne Monette, MD, MSc,‡‖¶ Nicolas Noiseux, MD,# Louis P. Perrault, MD, PhD,** Karen P. Alexander, MD,†† Yves Langlois, MD,§ Nandini Dendukuri, PhD,† Patrick Chamoun, RRT,§ Georges Kasparian, BSc,‡‡ Sophie Robichaud, RRT,** S. Michael Gharacholou, MD,†† Jean-François Boivin, MD, ScD†‡

Montreal, Quebec, Canada; and Durham, North Carolina

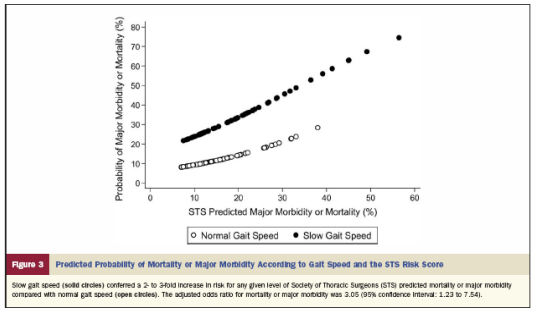


Figure 3 Predicted Probability of Mortality or Major Morbidity According to Gait Speed and the STS Risk Score

Slow gait speed (solid circles) conferred a 2- to 3-fold increase in risk for any given level of Society of Thoracic Surgeons (STS) predicted mortality or major morbidity compared with normal gait speed (open circles). The adjusted odds ratio for mortality or major morbidity was 3.05 (95% confidence interval: 1.23 to 7.54).

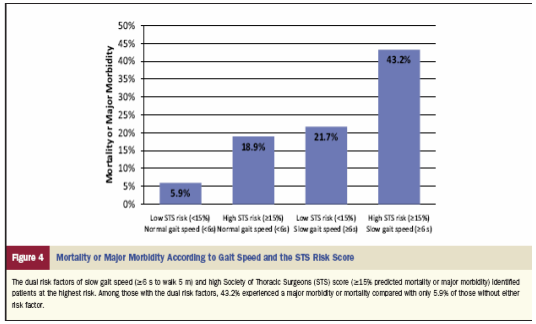


Figure 4 Mortality or Major Morbidity According to Gait Speed and the STS Risk Score

The dual risk factors of slow gait speed (≥6 s to walk 5 m) and high Society of Thoracic Surgeons (STS) score (≥15% predicted mortality or major morbidity) identified patients at the highest risk. Among those with the dual risk factors, 43.2% experienced a major morbidity or mortality compared with only 5.9% of those without either risk factor.

Table 4 Incremental Value of Gait Speed Above the STS Risk Score to Predict Mortality or Major Morbidity

Variables Entered in Model	Model Without Gait Speed	Model With Gait Speed
Variables entered in model*		
STS risk score	1.06 (1.02–1.11)	1.05 (1.004–1.10)
Slow gait speed	—	3.05 (1.23–7.54)
Model performance		
AIC	137	133
BIC	−496	−497
Hosmer-Lemeshow chi-square†	11.53 (0.17)	10.29 (0.25)
AUC‡	0.70 (0.60–0.80)	0.74 (0.64–0.84)
IDI‡	5% (1%–9%)	

Improved model performance is suggested by a decrease in AIC, BIC, Hosmer-Lemeshow chi-square; an increase in AUC; and a positive IDI (24,25). STS risk score indicates the predicted risk of mortality or major morbidity according to the STS risk score (percentage). *Expressed as odds ratio (95% CI). †Expressed as value (p value). ‡Expressed as value (95% CI).

Abbreviations as in Tables 1 and 3.

5 meter walking speed dichotomized at 6 sec= about 0.83 m/sec

PostOP Morbidity= stroke, renal failure, prolonged ventilation, deep infections or need for reoperation

Surgical risk score with > 30 factors

Table 3. Final List of Candidate Variables and Coding For STS Risk Models

Candidate Variables	Coding
Continuous variables	
Age[a]	Linear spline with knots at 50 and 60.
Ejection fraction[a]	Linear; values > 50 are mapped to 50. Only 0.03% of patients have ejection fraction < 10, and that is presumed to be a data entry error; these values are considered invalid and are treated like missing data. The decision to consolidate values > 50 was based on initial exploratory analyses in which data were used to suggest the functional form of continuous variables.
Body surface area[a]	Quadratic polynomial modeled separately for males and females. Note: body surface areas < 1.4 and > 2.6 were mapped to these values, respectively.[c]
Creatinine[a]	Linear spline with knots at 1.0 and 1.5. (Only for patients not on dialysis.) Note: Creatinine values < 0.5 and > 5.0 were mapped to these values, respectively.[d]
Time trend[a]	Ordinal categorical variable with separate category for each 6-month harvest interval.
Binary variables	
Dialysis[a]	Yes/no
Preoperative atrial fibrillation[b]	Yes/no
Shock	Yes/no
Female[a]	Yes/no
Hypertension	Yes/no
Immunosuppressive treatment	Yes/no
Percutaneous coronary intervention ≤ 6 hours	Yes/no
Preoperative intra-aortic balloon pump or inotropes	Yes/no
Peripheral vascular disease	Yes/no
Unstable angina (no myocardial infarction < 7 days)	Yes/no
Left main disease	Yes/no
Aortic stenosis	Yes/no
Aortic insufficiency	Defined as at least moderate (yes/no)
Mitral insufficiency	Defined as at least moderate (yes/no)
Tricuspid insufficiency	Defined as at least moderate (yes/no)
Categorical variables	
Chronic lung disease	4 groups: (1) none, (2) mild, (3) moderate, (4) severe
CVD/CVA	3 groups: (1) no CVD, (2) CVD no CVA, (3) CVD + CVA
Diabetes mellitus	3 groups: (1) insulin diabetes, (2) noninsulin diabetes, (3) other or no diabetes
Number diseased coronary vessels	3 groups: (1) fewer than 2 diseased vessels, (2) 2 disease vessels, (3) 3 diseased vessels; modeled as linear across the categories.
Myocardial infarction	4 groups: (1) ≤ 6 hours, (2) > 6 and < 24 hours, (3) 1 to 21 days, (4) > 21 days or no myocardial infarction.
Race	4 groups: (1) black, (2) Asian, (3) Hispanic, (4) other, including Caucasian
Status	4 groups: (1) elective, (2) urgent, (3) emergent, no resuscitation, (4) salvage or emergent with resuscitation
Previous cardiovascular operations	3 groups: 0 previous, 1 previous, 2 or more previous
CHF and NYHA class	3 groups: no CHF, CHF not NYHA IV, CHF + NYHA IV
Interactions	
Age by reoperation[a]	
Age by emergent status[a]	

Gait speed alone did as well as 30+ factor risk score

Both together were better than either alone

PSYCHOMOTOR SLOWING

ELSEVIER

Acta Psychologica 86 (1994) 199–225

acta psychologica

Processing speed as a mental capacity

Robert Kail [a,*], Timothy A. Salthouse [b]

[a] *Dept. of Psychological Sciences, Purdue University, West Lafayette, IN 47907, USA*
[b] *School of Psychology, Georgia Institute of Technology, Atlanta, GA 30332, USA*

Abstract

Throughout the lifespan, there are pronounced age differences in speed of processing, differences that are consistently related to performance on measures of higher-order cognition. In this article, we examine domain-specific and global explanations of these age differences in processing speed; we conclude that although experience can play a role in age differences in speed, there is also evidence that a general mechanism limits speeded performance. We also review research that shows the influence of processing speed on the quality of performance on nonspeeded tasks such as reasoning and memory. We suggest that speed of processing should be viewed as a fundamental part of the architecture of the cognitive system as it develops across the entire lifespan.

- Controversial concept
- Is processing speed an indicator of fundamental brain function?
- What is actually being measured: perception, retrieval, movement initiation….?

Digit symbol substitution test

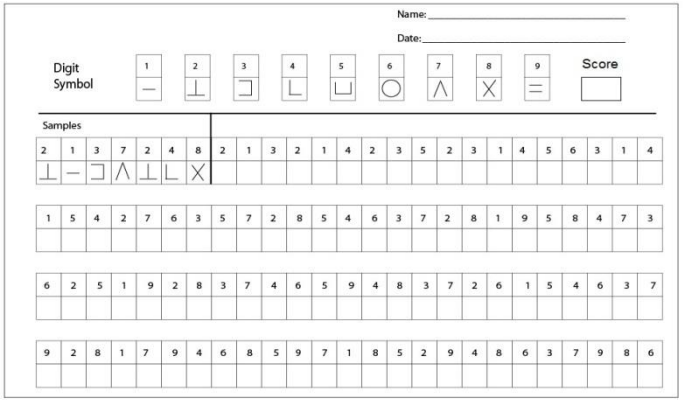


Figure 13.1 The Digit Symbol Substitution Test (DSST). The athlete completes as many boxes as possible in 90 seconds

Psychomotor slowing and Incident TMF

CHS data

Table XXX: Longitudinal association between year 5 DSST and year 6-11 cumulative incident thinking, moving and feeling outcomes: odds ratio or *regression coefficient* and significance

Nature of Analysis, Outcome Time and Year 5 DSST	Thinking Outcome 3MSE				Moving Outcome Gait Speed (m/s)				Feeling Outcome CES-D			
	Conti-nuous	Full Syndrm (<80)	Subsyn (80-85)	Unclssfd	Conti-nuous	Full Syndrm (<0.6)	Subsyn (0.6-1.0)	Unclssfd	Conti-nuous	Full Syndrm (11+)	Subsyn (5-10)	Unclssfd
Unadjusted Year 6-11												
DSST (raw)	NA	0.89***	0.91***	0.96***	NA	0.94***	0.96***	0.94***	NA	0.95***	0.97***	0.96***
DSST ≤29	NA	40.8***	29.0***	6.07***	NA	23.1***	10.1***	25.5***	NA	16.4***	7.89***	10.8***
30-39	NA	5.97***	6.91***	2.33***	NA	2.54***	1.98**	3.36***	NA	2.13**	1.59	1.89**
40-48	NA	1.97***	3.22***	1.61***	NA	1.50	1.53*	2.26***	NA	1.76*	1.33	1.31
>48	NA	1.0 (ref)	1.0 (ref)	1.0 (ref)	NA	1.0 (ref)	1.0 (ref)	1.0 (ref)	NA	1.0 (ref)	1.0 (ref)	1.0 (ref)
Adjusted for Covariate Set 1 Year 6-11												
DSST (raw)	NA	0.92***	0.94***	0.97***	NA	0.95***	0.97***	0.94***	NA	0.98	0.99	0.98
DSST ≤29	NA	13.9***	9.48***	4.27***	NA	15.5**	7.91**	19.8***	NA	4.25**	3.15**	4.32***
30-39	NA	3.15***	3.46***	1.87***	NA	2.38**	1.89*	2.87**	NA	1.16	1.04	1.30*
40-48	NA	1.40	2.01***	1.45***	NA	1.47	1.52	2.18**	NA	1.31	1.09	1.10
>48	NA	1.0 (ref)	1.0 (ref)	1.0 (ref)	NA	1.0 (ref)	1.0 (ref)	1.0 (ref)	NA	1.0 (ref)	1.0 (ref)	1.0 (ref)
Adjusted for Covariate Set 1+2 Year 6-11												
DSST (raw)	NA	0.93***	0.95***	0.97***	NA	0.96**	0.97**	0.94***	NA	0.98	0.99	0.99
DSST ≤29	NA	9.95***	6.69***	3.58***	NA	9.09**	7.55*	18.1***	NA	5.27**	3.80*	4.98**
30-39	NA	2.43***	2.65***	1.69***	NA	1.75	1.83	2.66**	NA	1.10	1.02	1.23
40-48	NA	1.20	1.81***	1.35***	NA	1.32	1.67*	2.17**	NA	1.34	1.15	1.13
>48	NA	1.0 (ref)	1.0 (ref)	1.0 (ref)	NA	1.0 (ref)	1.0 (ref)	1.0 (ref)	NA	1.0 (ref)	1.0 (ref)	1.0 (ref)

Covariate set 1=3MSE, gait speed and CES-D at year 5; set 2=Age, gender, race, diabetes, hypertension, AAI and education; *p<0.10; **p<0.05; ***p<0.01

Variability

Key Concepts of Variable Performance across the lifespan

- In addition to mean performance, variability in cognitive and movement performance differs across the lifespan.
- Change in variability or increased variability under stress may be early/subclinical indicators of a changing neurological system.

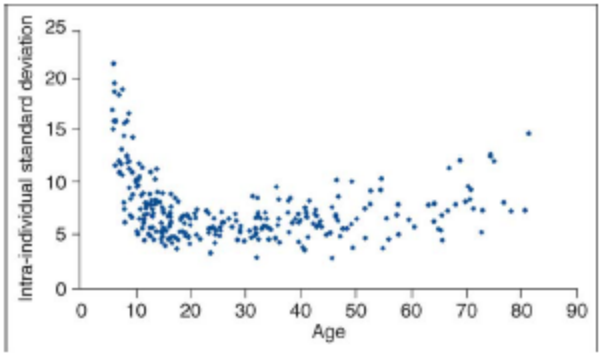


Figure 1. Intra-individual variability across the lifespan. Choice reaction time (CRT) was assessed across 32 trials for 273 participants aged 6–81 years. Potential confounds including practice effects across trials, age-related differences in mean performance level, and their interaction were first removed from the raw CRT data using a regression procedure. The residual scores from this regression were linearly transformed as t-scores with a mean of 50 and standard deviation of 10 across all data points. Intra-individual standard deviations were subsequently computed across the 32 CRT trials. The relationship between age and inconsistency across the lifespan was characterized by a U-shaped function, with advancing age throughout childhood, adolescence, and young adulthood associated with decreasing variability. By contrast, increasing age throughout older adulthood was linked to increasing variability. Reproduced, with permission, from Ref. [10].

MacDonald 2006 Trends in Neuroscience

Gait Variability

Jennifer S. Brach, PhD, PT, GCS
NIA Beeson Scholar
Department of Physical Therapy
University of Pittsburgh

regular

irregular

Gait Variability is irregularly irregular timing and spacing of steps

Aspects of Gait Variability and Aging Brach et al

Stance Time Variability Predicts Decline in Mobility

Model	HR (CI)	P
1	1.26 (1.15, 1.37)	<.0001
2	1.15 (1.04, 1.27)	.007
3	1.13 (1.02, 1.25)	.02
4	1.13 (1.01, 1.27)	.03

Model 1: Stance time variability

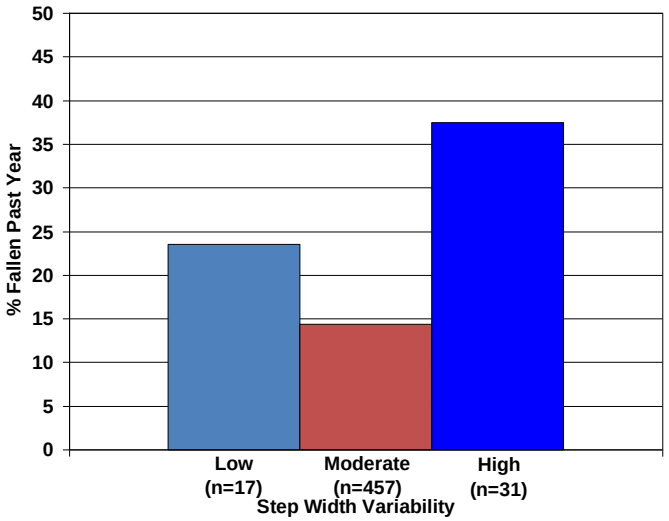
Model 2: Model 1 + gait speed

Model 3: Model 2+ age, gender, and race

Model 4: Model 3 + chronic conditions, medications, health status, physical activity

Brach et al, 2007

Step Width Variability and Fall History



Contributors to Variable Gait

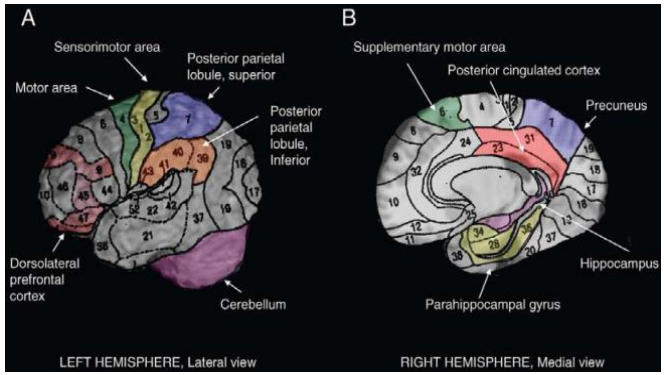
(linear regressions adjusted for age, gender, and race)

	Stance Time Variability	Step Length Variability	Step Width Variability
CNS			
3MS	■		
Finger Tap	■		
Trails A	■		
Trails B	■		
DSST	■		
Sensory			
Vibration			■
Vision			■
Strength			
Grip	■		
Chair stand	■		
LE pain			
Depression	■	■	■

Brain and gait

Rosano et al J Gerontol A Biol Sci Med Sci. 2008

Shorter steps and longer double support times were associated with smaller sensorimotor regions and also with smaller frontoparietal regions within the motor, visuospatial, and

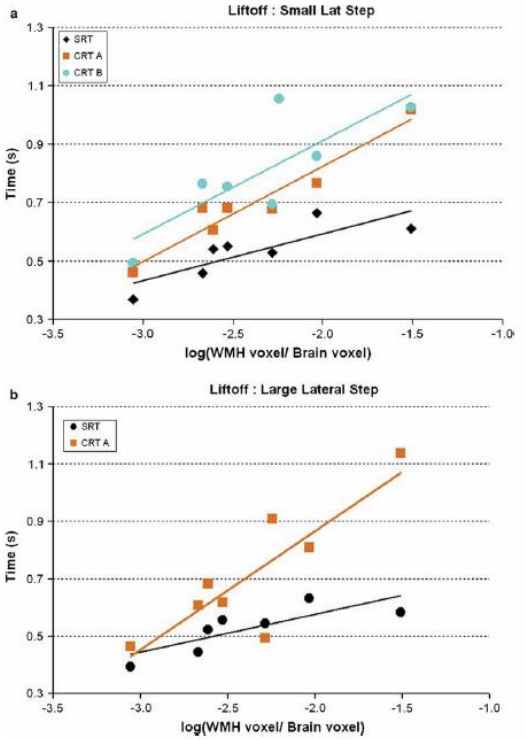


Rosano Neuroepidemiology 2007

	Odds ratios		
	brain infarct ≥1 (n = 82)	basal ganglia infarct ≥1 (n = 60)	WMH ≥3 (n = 104)
Quartiles of stance time variability			
1st (CV <3.6)	2.3 (1.1–5.1)	2.3 (0.9–5.8)	1.5 (0.7–3.4)
2nd (CV 3.6–4.5)	1.0	1.0	1.0
3rd (CV 4.6–5.9)	1.9 (0.8–4.2)	2.0 (0.8–5.2)	1.63 (0.8–3.5)
4th (CV >5.9)	2.9 (1.3–6.3)	3.2 (1.3–7.8)	1.96 (0.9–4.2)

Sparto et al Exp Brain Res. 2008

Step initiation is prolonged as task complexity and white matter burden increase



Gait variability is associated with subclinical brain vascular abnormalities

BLSA approach to gait and cognition

Qu (Teresa) Tian

Central nervous system:
Frontal, sensorimotor, parietal, subcortical, cerebellum

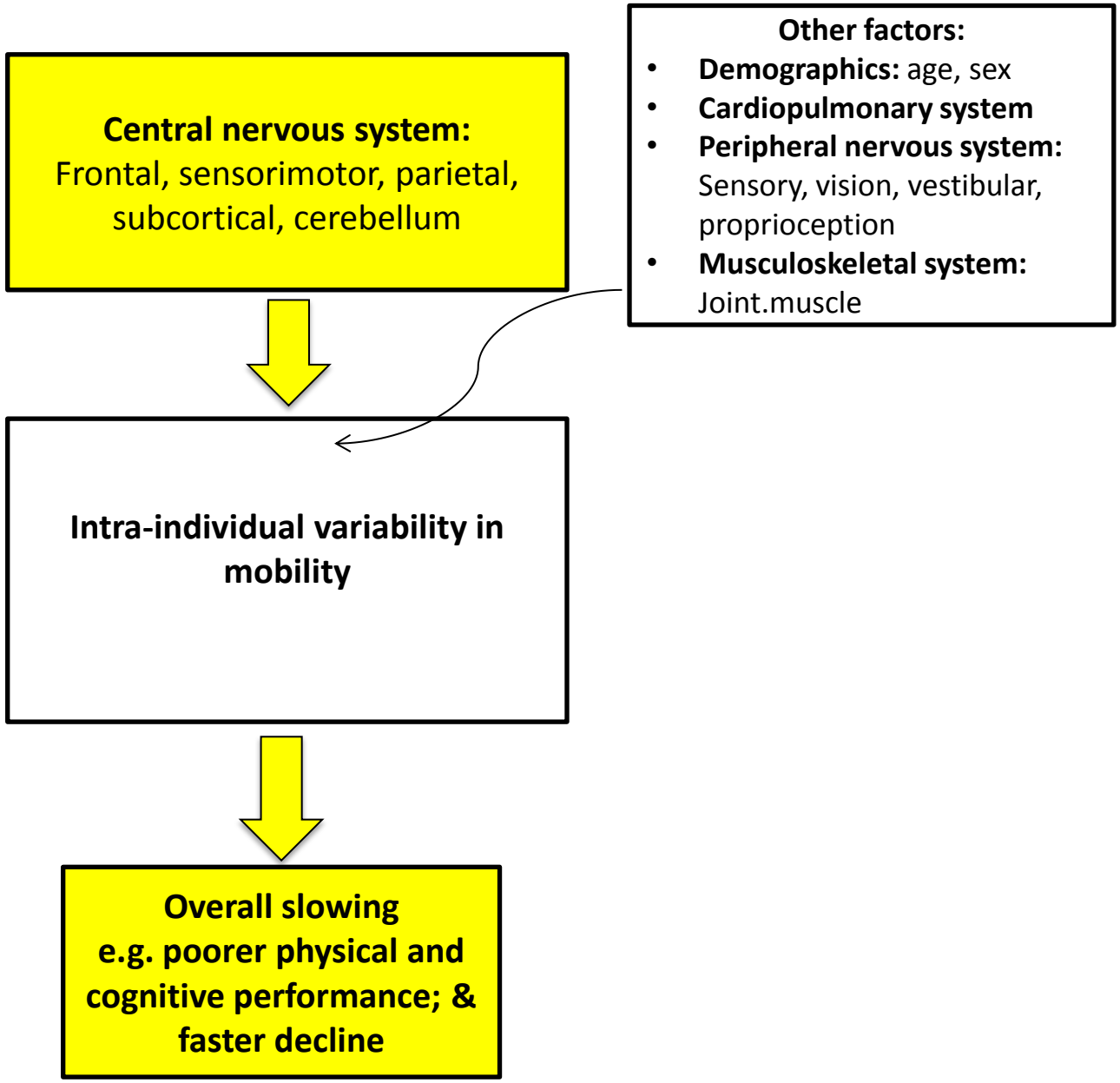
Other factors:
- **Demographics:** age, sex
- **Cardiopulmonary system**
- **Peripheral nervous system:** Sensory, vision, vestibular, proprioception
- **Musculoskeletal system:** Joint,muscle

Increased intra-individual variability in performance

Overall slowing
e.g. poorer physical and cognitive performance; & faster decline

Tian, Q. & Studenski S.

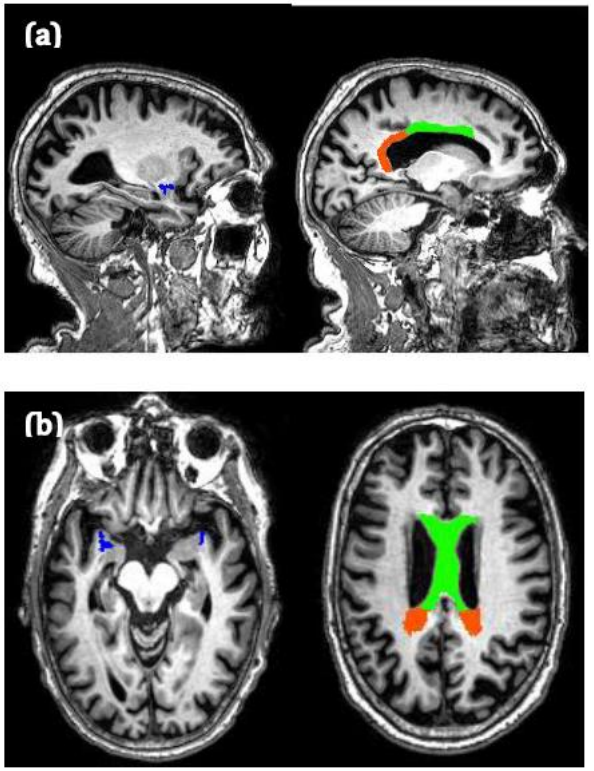
1. Neural correlates of walking speed



1.1 Lower focal WM microstructural integrity is associated with slower walking speed.

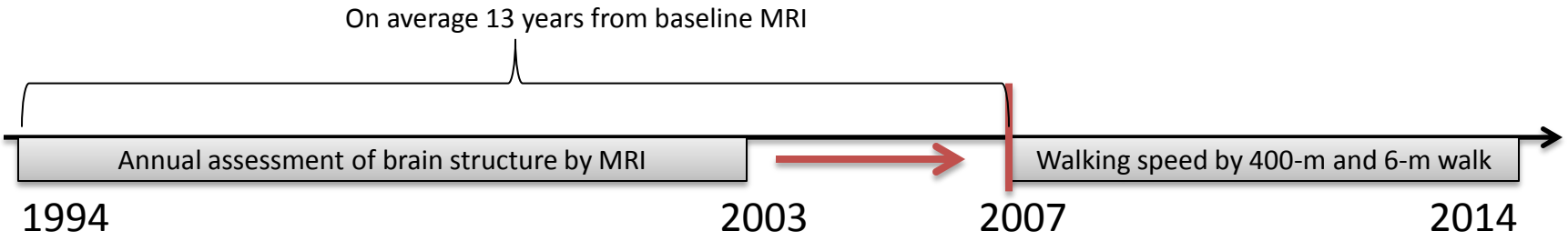
- **Lower fractional anisotropy in the inferior fronto-occipital fasciculus, the uncinate fasciculus, the body and the splenium of the corpus callosum was associated with slower walking speed (n=502). Associations were independent of age, sex, height, and weight. (Mean age = 68 yrs)**

Independent variables: Fractional anisotropy in selected tracts	Dependent variable: Mean lap time (log transformed value) β (95% CI), p-value
Inferior fronto-occipital fasciculus	-0.015 (-0.029, -0.001) 0.032
Superior longitudinal fasciculus	-0.011 (-0.024, 0.002) 0.099
Uncinate fasciculus	-0.019 (-0.032, -0.006) 0.005
Genu of corpus callosum	-0.013 (-0.028, 0.002) 0.094
Body of corpus callosum	-0.024 (-0.038, -0.010) 0.001
Splenium of corpus callosum	-0.019 (-0.033, -0.005) 0.009



Tian et al. 2015 (under review)

1.2 Greater atrophy in the entorhinal cortex was prospectively associated with slower walking speed.

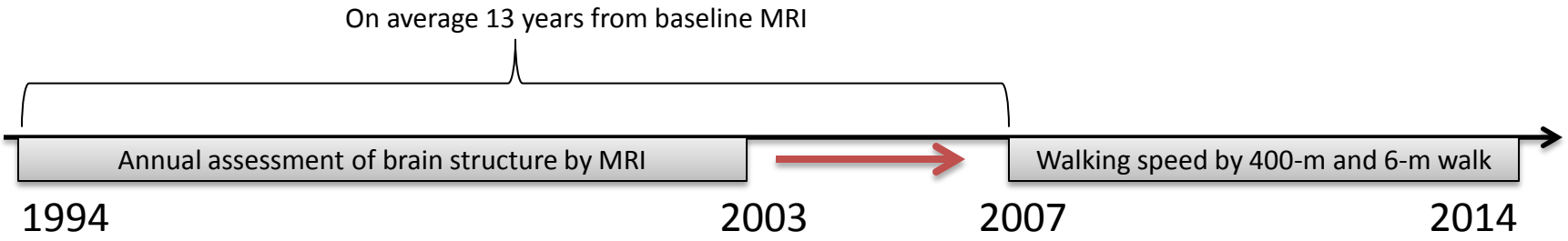


Greater atrophy in the entorhinal cortex was associated with longer time to complete 400m (β=-0.0002, p=0.002), and with slower gait speed at a usual pace (β=0.033, p=0.018) and slower gait speed at a fast pace (β=0.027, p=0.001).

	Time to complete 400-m (n=64)		**Usual gait speed on 6-m (n=96)**		**Fast gait speed on 6-m (n=94)**	
	time	Time*interval	gait speed	speed*interval	gait speed	speed*interval
			β (SE), p-value			
Middle frontal gyrus	-0.002 (0.006) 0.702	-0.000 (0.000) 0.201	2.568 (1.170) 0.031	0.144 (0.096) 0.136	1.125 (0.775) 0.150	0.073 (0.057) 0.204
Hippocampus	-0.000 (0.001) 0.868	0.000 (0.000) 0.284	0.138 (0.200) 0.484	-0.011 (0.015) 0.466	-0.018 (0.130) 0.889	-0.003 (0.009) 0.763
Parahippocampus	-0.001 (0.001) 0.502	0.000 (0.000) 0.134	-0.025 (0.125) 0.845	0.018 (0.012) 0.145	-0.027 (0.081) 0.738	0.007 (0.008) 0.329
Entorhinal cortex	0.0005 (0.0008) 0.5017	-0.0002 (0.0001) 0.0022	-0.213 (0.146) 0.148	0.033 (0.014) 0.018	-2.082 (0.095) 0.031	0.027 (0.008) 0.001
Perirhinal cortex	-0.0008 (0.001) 0.386	-0.0001 (0.0001) 0.1701	0.097 (0.194) 0.620	0.019 (0.019) 0.312	0.131 (0.127) 0.308	0.020 (0.011) 0.075

Tian et al. (in preparation)

1.3 Greater atrophy in the entorhinal cortex was prospectively associated with faster decline in walking speed.

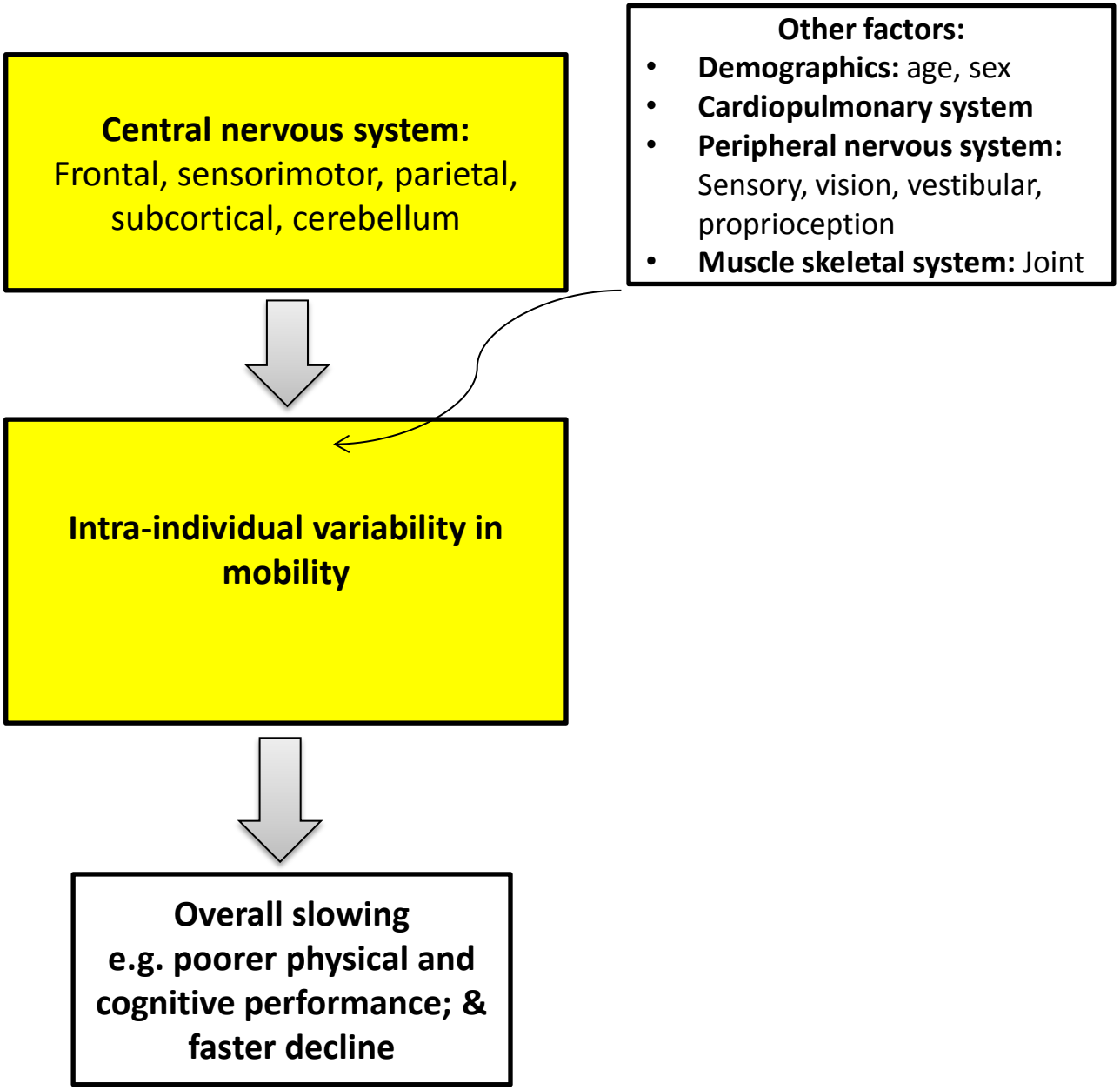


Greater atrophy in the entorhinal cortex was associated with greater increase in time to complete 400m (β, p=), and with greater decline in usual gait speed (β=0.033, p=0.018).

	Change in time to complete 400m		Decline in usual gait speed		Decline in fast gait speed	
	slope	slope*interval	slope	slope*interval	slope	Slope*interval
			β (SE), p-value			
Middle frontal gyrus	0.044 (0.048) 0.359	-0.003 (0.003) 0.307	11.626 (39.218) 0.768	-0.461 (3.084) 0.882	-6.463 (13.730) 0.639	1.049 (1.082) 0.336
Hippocampus	0.007 (0.007) 0.319	0.0004 (0.0005) 0.465	2.473 (6.438) 0.702	-0.840 (0.462) 0.073	0.304 (1.453) 0.835	0.066 (0.142) 0.642
Parahippocampus	0.005 (0.004) 0.286	0.0001 (0.0004) 0.812	-0.326 (4.084) 0.937	-0.257 (0.385) 0.507	0.304 (1.453) 0.835	0.066 (0.142) 0.642
Entorhinal cortex	0.006 (0.006) 0.324	-0.001 (0.001) 0.041	-3.011 (4.810) 0.533	1.049 (0.433) 0.018	-1.576 (1.691) 0.354	0.198 (0.161) 0.223
Perirhinal cortex	0.010 (0.008) 0.188	-0.0001 (0.001) 0.894	7.143 (6.301) 0.261	0.224 (0.596) 0.708	-1.365 (2.274) 0.550	0.183 (0.215) 0.398

Tian et al. (in preparation)

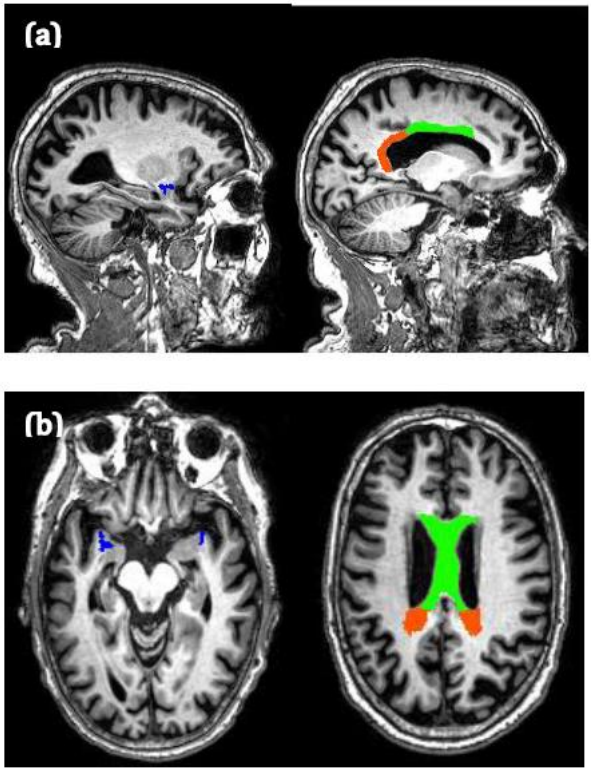
2. Neural correlates of walking variability



2.1 Lower focal WM microstructural integrity was associated with higher walking variability (laptime variation (sd in seconds) across 10 laps of the 400 meter walk)).

- **Lower fractional anisotropy in the uncinate fasciculus, the body and the splenium of the corpus callosum was associated with higher lap time variation (n=502). Associations were independent of age, sex, height, and weight.**

Independent variables: Fractional anisotropy in selected tracts	Lap time variation (log transformed value) β (95% CI), p-value
Inferior fronto-occipital fasciculus	-0.031 (-0.073, 0.010) 0.137
Superior longitudinal fasciculus	0.001 (-0.038, 0.039) 0.973
Uncinate fasciculus	-0.038 (-0.077, 0.000) 0.050
Genu of corpus callosum	-0.020 (-0.065, 0.024) 0.372
Body of corpus callosum	-0.048 (-0.089, -0.007) 0.022
Splenium of corpus callosum	-0.054 (-0.095, -0.013) 0.010



Figures prepared by Venkatraman, V.

Tian et al. 2015 (under review)

2.2.1 Lower GM microstructural integrity was associated with higher walking variability.

- **Gray matter mean diffusivity in selected regions of interest added significant contribution to lap time variation, over and beyond age, sex, height, and weight (n=451). Age ≥ 50 yrs**

Table 2
Hierarchical regression analyses with initial entry of demographic variables related to lap time variation (n=451).

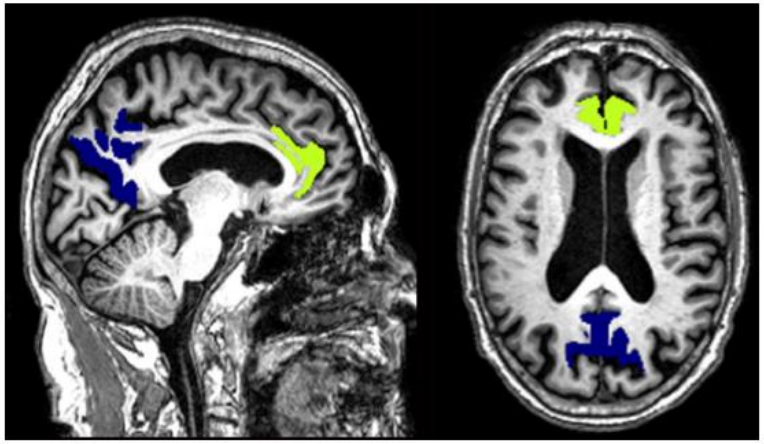
Blocks of predictors	R^2	ΔR^2	F change	Sig. of F change
1. Age, sex, height, and weight	0.154	0.154	20.149	<0.001
2. Average of MD in ROIs	0.169	0.016	8.250	0.004

MD=mean diffusivity. ROIs=regions of interest.

Tian et al. (in preparation)

2.2.2 Lower focal GM microstructural integrity was associated with higher walking variability.

- Higher gray matter mean diffusivity in the precuneus, the anterior and middle cingulate cortices was strongly associated with high lap time variation.
- Associations persisted after adjustment for age, sex, height, weight, health conditions, and mean lap time.
- These integrating areas subserve a variety of behavioral functions.



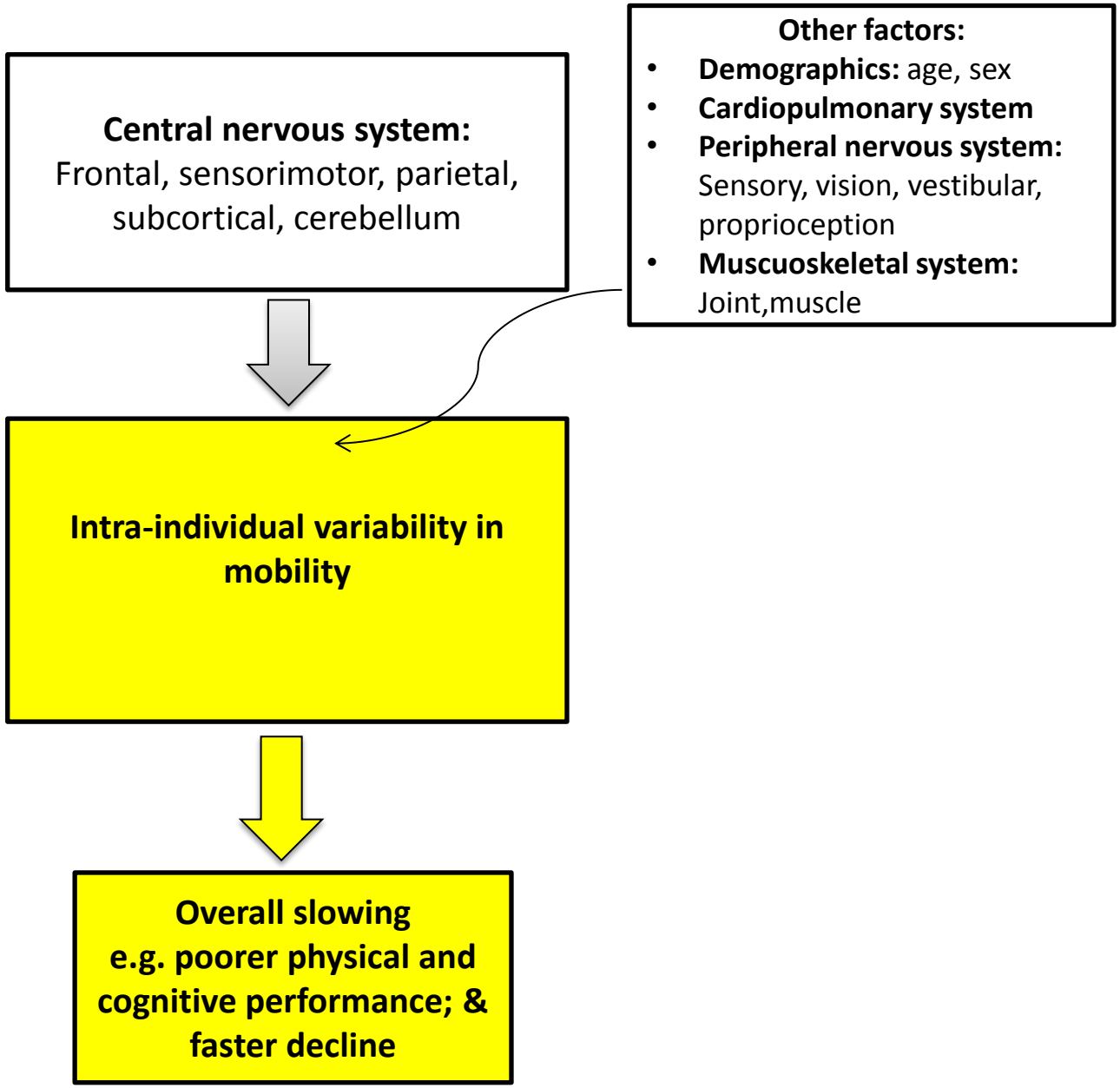
Figures prepared by Venkatraman, V.

Tian et al. (in preparation)

Function domain	Gray matter regions	Model 1: Adjusted for age, sex, height, and weight	Model 2: Model 1+ Hypertensions and diabetes	Model 3: Model 1+ mean lap time
Multi-modal areas	Precuneus	0.087** (0.034, 0.139) 0.001	0.088 (0.035, 0.140) 0.001	0.055 (0.005, 0.104) 0.031
	Posterior cingulate gyrus	0.065 (0.009, 0.121) 0.024	0.070 (0.013, 0.126) 0.016	0.037 (-0.015, 0.090) 0.164
Sensori-motor function	Precentral gyrus	0.022 (-0.021, 0.065) 0.310	0.020 (-0.023, 0.063) 0.359	0.013 (-0.027, 0.053) 0.519
	Postcentral gyrus	0.033 (-0.010, 0.077) 0.134	0.031 (-0.013, 0.076) 0.168	0.017 (-0.024, 0.058) 0.403
	Supplementary motor cortex	0.042 (-0.002, 0.085) 0.063	0.039 (-0.005, 0.084) 0.082	0.030 (-0.011, 0.071) 0.149
	Putamen	0.025 (-0.020, 0.071) 0.274	0.026 (-0.020, 0.073) 0.265	0.006 (-0.037, 0.048) 0.800
	Caudate	0.037 (-0.007, 0.081) 0.095	0.038 (-0.006, 0.082) 0.090	0.022 (-0.019, 0.063) 0.300
	Thalamus Proper	0.044 (-0.003, 0.090) 0.064	0.046 (0.000, 0.093) 0.052	0.014 (-0.029, 0.058) 0.520
	Middle cingulate gyrus	0.078** (0.029, 0.127) 0.002	0.077 (0.028, 0.126) 0.002	0.056 (0.010, 0.102) 0.017
Executive function	Middle frontal gyrus	0.016 (-0.031, 0.064) 0.502	0.013 (-0.034, 0.061) 0.582	0.009 (-0.035, 0.053) 0.698
	Superior parietal lobe	0.045 (0.002, 0.087) 0.041	0.041 (-0.002, 0.085) 0.063	0.027 (-0.013, 0.067) 0.191
	Anterior cingulate gyrus	0.075** (0.027, 0.123) 0.002	0.076 (0.028, 0.124) 0.002	0.057 (0.012, 0.102) 0.013
Memory	Hippocampus	0.062 (0.003, 0.121) 0.038	0.064 (0.005, 0.123) 0.033	0.041 (-0.014, 0.096) 0.148
	Parahippocampal gyrus	0.058 (0.008, 0.107) 0.023	0.057 (0.007, 0.106) 0.026	0.029 (-0.017, 0.076) 0.216
	Entorhinal area	0.026 (-0.019, 0.071) 0.252	0.027 (-0.018, 0.072) 0.237	0.021 (-0.021, 0.063) 0.326
	Amygdala	0.043 (-0.002, 0.087) 0.059	0.043 (-0.002, 0.087) 0.061	0.027 (-0.015, 0.068) 0.204

**p≤0.003 (Bonferroni adjusted). Values of lap time variation were log transformed due to skewed distribution. Mean diffusivity was in standardized units.

3. Associations between variability and slowing, cross-sectionally and longitudinally



3.1.1 Higher lap time variation was cross-sectionally associated with poorer psychomotor speed, measured by Trail Making Test – part A

Table 2. Regression models of lap time variation predicting executive function measures that were significant at $p < 0.05$, standardized unit

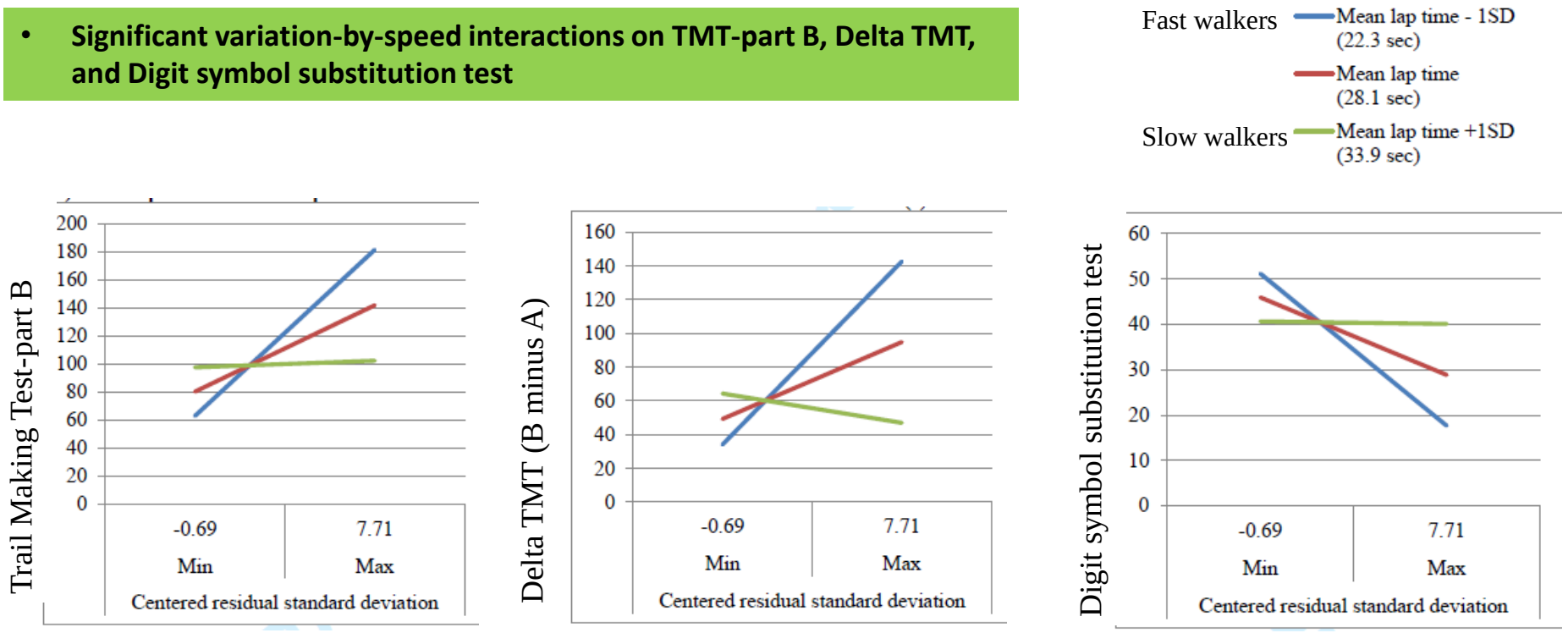
	Unadjusted	Model 1: adjusted for mean lap time	Model 2: adjusted for mean lap time, age, sex, and education
		β (95% CI), p-value	
Time to perform part A of TMT (n = 662)	0.242 (0.154, 0.330) <0.001	0.119 (0.024, 0.213) 0.014	0.113 (0.022, 0.204) 0.015
Time to perform part B of TMT (n = 645)	0.173 (0.081, 0.265) <0.001	0.040 (-0.059, 0.139) 0.431	0.041 (-0.055, 0.137) 0.399
Delta TMT (n = 645)	0.129 (0.036, 0.222) 0.006	0.014 (-0.086, 0.115) 0.779	0.017 (-0.081, 0.116) 0.732
DSST (n = 741)	-0.195 (-0.279, -0.110) <0.001	-0.044 (-0.134, 0.046) 0.336	-0.026 (-0.107, 0.054) 0.525

Note: TMT = Trail Making Test; DSST = Digit symbol substitution test.

Tian et al. (2015) Age and Ageing

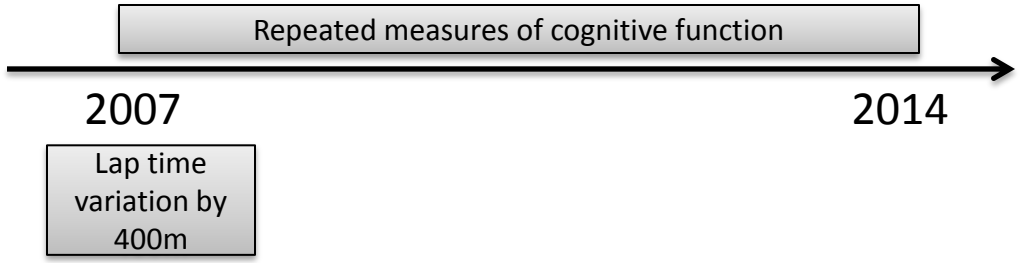
3.1.2 Higher lap time variation appeared to be associated with poorer cognitive function <u>involved with cognitive flexibility</u> in faster walkers only.

- **Significant variation-by-speed interactions on TMT-part B, Delta TMT, and Digit symbol substitution test**



Tian et al. (2015) Age and Ageing

3.2 Higher lap time variation was prospectively associated with greater increase in Trail Making Test – part B, and Delta TMT (B-A)

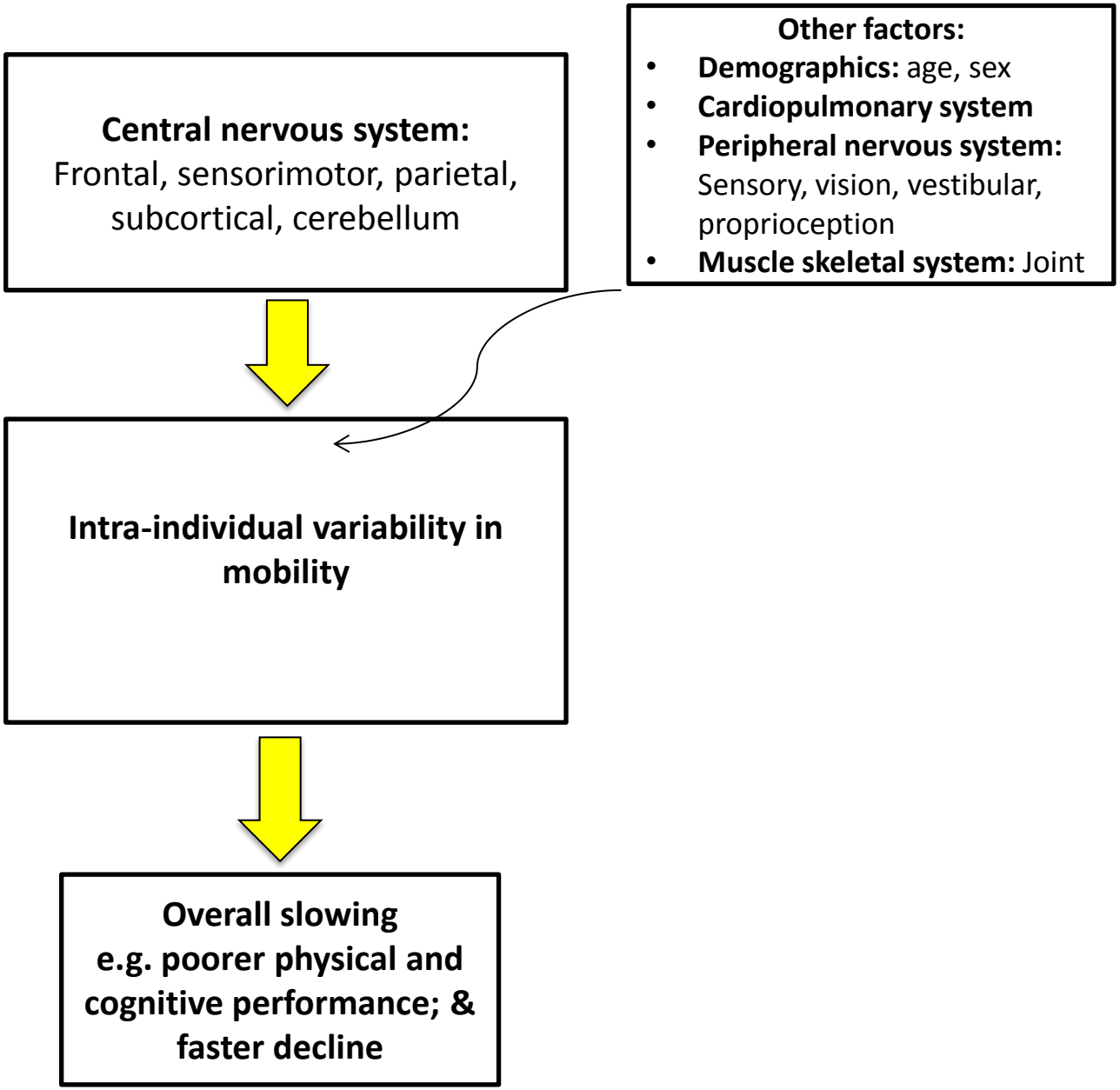


	n	Lap time variation	variation*interval
		β (SE), p-value	
Trail A	662	2.204 (1.115)	0.257 (0.355)
		0.048	0.471
Trail B	645	-0.511 (4.091)	3.360 (0.976)
		0.901	<0.001
Delta TMT	645	-0.725 (3.564)	2.918 (0.970)
		0.839	0.003
DSST	741	-0.358 (0.927)	-0.144 (0.164)
		0.700	0.380

Model: cognition = intercept + age_at_baseline + sex + mean lap time + interval + age0*interval + sex*interval + **variation + variation*interval**

Tian et al. (in preparation)

4. WM –> variability -> speed



4. WM – Walking speed, mediated by walking variability

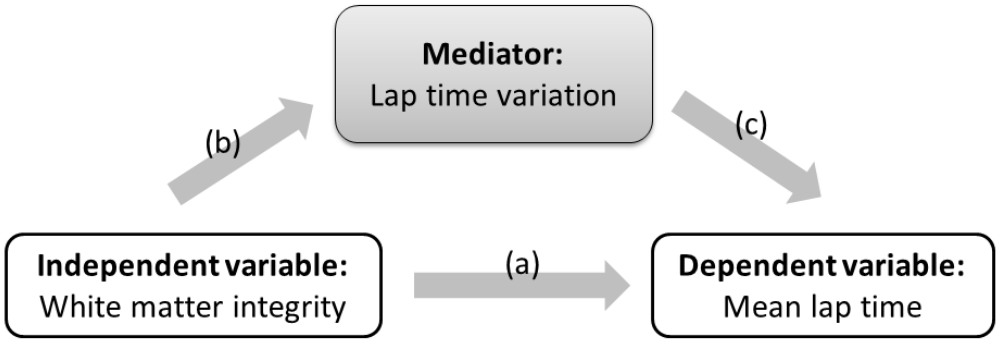


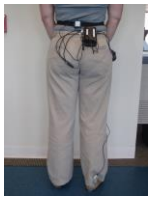
Table 2. Adjustment for lap time variation substantially and significantly attenuated the associations of fractional anisotropy in the uncinate fasciculus and body and splenium of corpus callosum with mean lap time (n=502)

	Total effect of independent variable on dependent variable	Effect of independent variable on dependent variable after adjusting for mediator	Change of regression coefficient, %	Sobel test for the significance of mediation
	Standardized β (SE) p-value			
Uncinate fasciculus	-0.019 (0.007) 0.005	-0.014 (0.006) 0.016	26.3%	.008
Body of corpus callosum	-0.024 (0.007) 0.001	-0.017 (0.006) 0.007	29.2%	.001
Splenium of corpus callosum	-0.019 (0.007) 0.009	-0.011 (0.006) 0.082	42.1%	.008

Note: Independent variable: fractional anisotropy; dependent variable: mean lap time (log transformed value); mediator: lap time variation. Models were adjusted for age, sex, height, and weight.

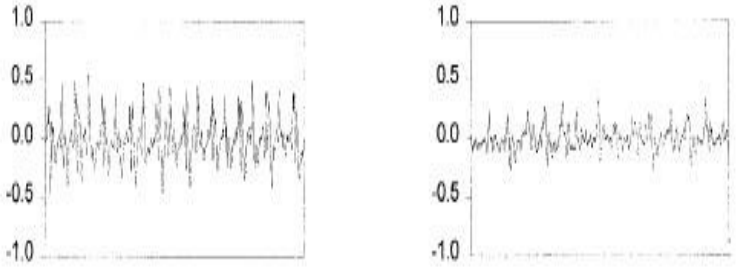
Tian et al. 2015 (under review)

Efficiency

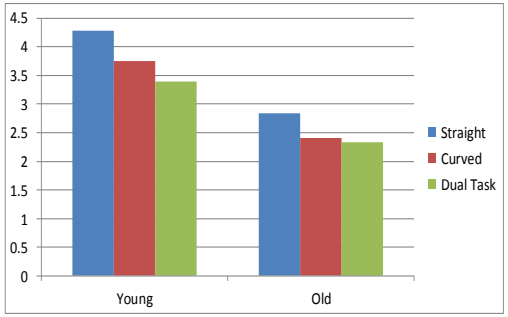


Brach New Direction: Smoothness

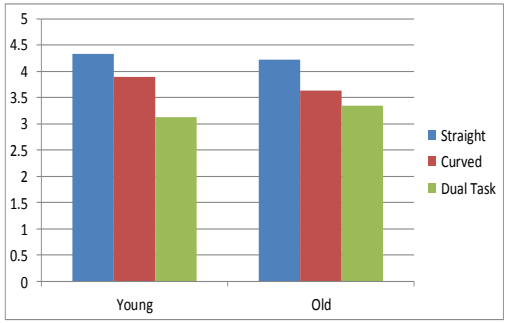
Linear acceleration used to calculate the **harmonic ratio** reflects the degree of <u>rhythm</u> of the acceleration signal



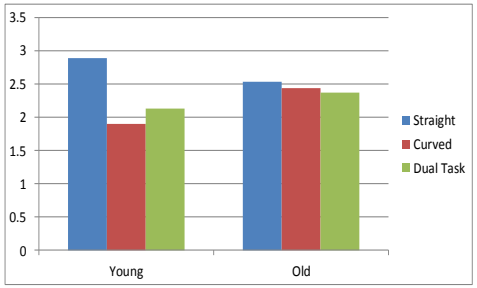
Harmonic Ratio: Effects of age and task



A-P



Vertical

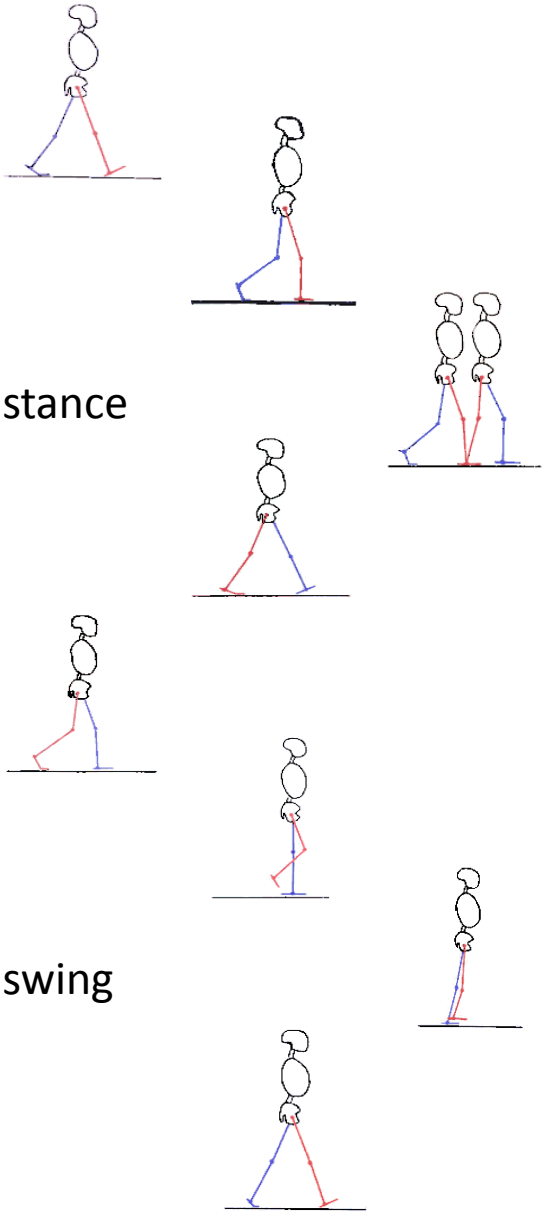


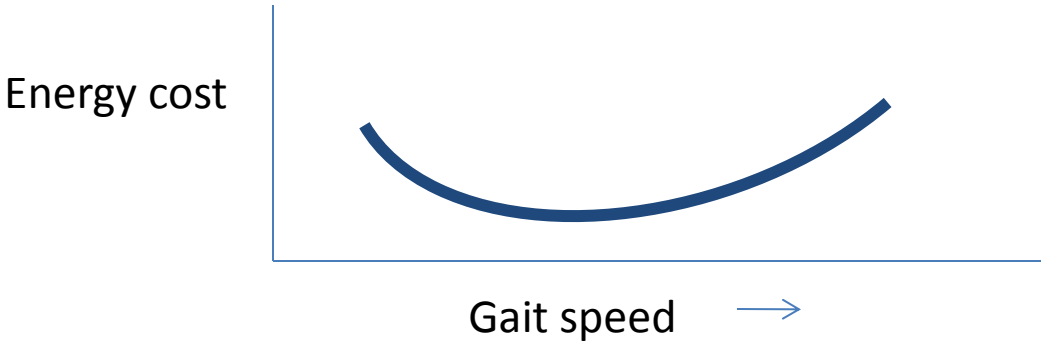
M-L

Brach et al J Gerontol A Biol Sci Med Sci. 2010

Smoothness, Gait Efficiency and the Energy Cost of Walking

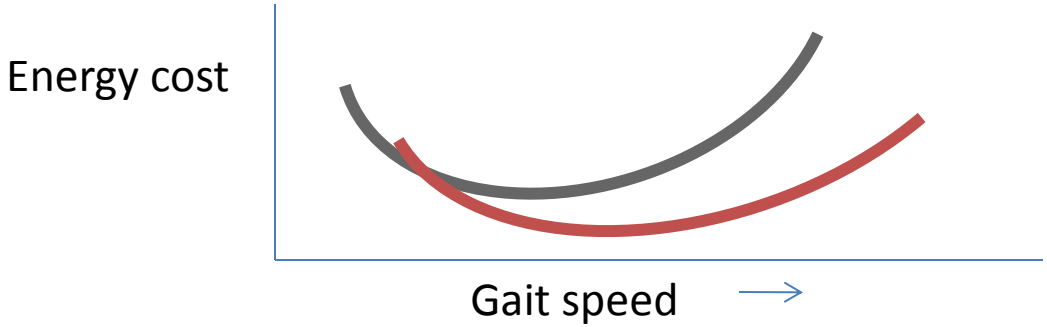
- Efficiency depends on optimal use of momentum and stored energy from the passive elements (pendulum effects) of movement cycles: pendulum base is foot during stance and hip during swing
- Changes in pace and stride length decrease energy efficiency
- There is a U shaped curve relating gait speed to energy use with an optimal nadir for gait efficiency. Slowing beyond optimal pace increases energy cost





Age, Gait Disorders and Gait Efficiency

- Age and gait disorders decrease gait efficiency
- With age, energy cost is higher at any gait speed
- Nadir for optimal efficiency moves to the left
- Can examine effect of biomechanical and motor control abnormalities on energy cost and efficiency
- Variability and loss of smoothness of movement are contributors to loss of efficiency….



RESERVE

Dual tasks assess brain reserve

- **Dual task paradigm**: compares performance on a single task to performance when also performing a second task. Decrements in performance are due to competition for brain resources (attention, processing) and can differ depending on the type of tasks.

The Cognition-Mobility Interface (COMBINE) is Associated with Cerebral Amyloid Deposition in Older Adults without Cognitive or Mobility Impairment.

Neelesh K. Nadkarni, Oscar Lopez, Stephanie A. Studenski, Beth E. Snitz, Subashan Perera, Ann D. Cohen, Chester A. Mathis, Robert Nebes, and William E. Klunk.

ACKNOWLEDGEMENTS:

Participants

Facilities: Pittsburgh Pepper Older American Independence Center (OAIC), pilot-funding.

Pittsburgh Alzheimer's Disease Research Center (ADRC).

University of Pittsburgh PET Research Center.

Hartford Center of Excellence in Geriatric Medicine.

Brain Aging & Cognitive Health Lab (Dr. Kirk Erickson), Dept. of Psychology, University of Pittsburgh

Personnel: G. Grove, C. Igne, Y. Kang, E. Halligan, R. Coleman and staff of OAIC, ADRC, PET and BACH centers.

BACKGROUND and HYPOTHESIS:

- Cognition and mobility are centrally integrated and functionally interrelated.
- The **co**gnition-**m**o**b**ility **in**terfac**e** **(COMBINE**) can be assessed by measuring the magnitude of change in performance of the two functions when performed at the same time relative to their performance measured separately.
- Tests of the COMBINE can serve as "stress-tests" to detect impending decline in well-functioning older adults and could therefore relate to amyloid deposition and neurodegeneration.

AIM:

The objective was to assess if changes in gait speed while performing four cognitive tasks is related to amyloid deposition and glucose metabolism in older adults without cognitive impairment and mobility problems.

METHODS: Participants

Inclusion criteria:

- Age: 65 to 85 yrs
- Walk independently, without use of assistive devices
- PET and MRI in the previous 18 months
- Met criteria for “cognitively unimpaired” based on parent study criteria

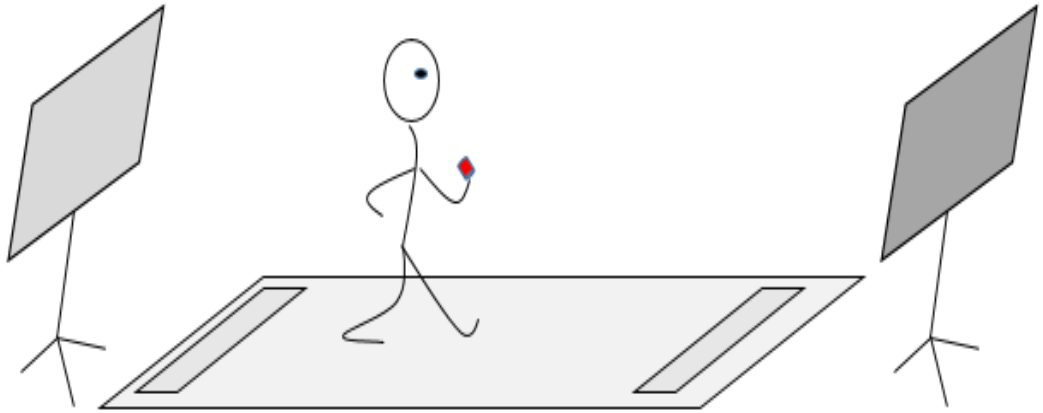
  (“Amyloid Pathology and Cognition in Normal Elderly Study”, 5R37AG025516, PI: Klunk)

Exclusion criteria:

- Prior falls
- Slow gait speed (< 0.6 m/sec)
- Significant hearing or visual impairment.
- Diagnosis of a neurological conditions, brain injury or any significant health condition that could interfere with mobility.
- Poor resting performance on experimental cognitive tasks (< 90%).

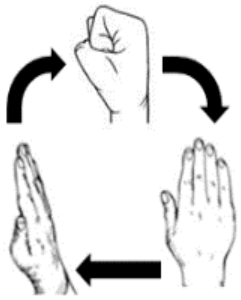
METHODS: Gait assessment : Regular walk & the COMBINE

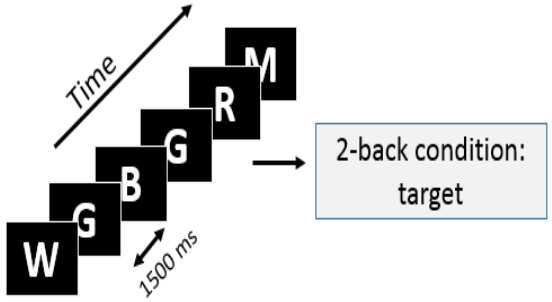
- Gait speed was assessed in regular walking condition and while performing cognitive tasks. "….. walk at you most comfortable pace …on a stroll"
- Gait Mat II: 8m long instrumented walkway.
- The primary variable of interest was change in regular gait speed while performing four cognitive tasks: 1) motor-sequencing, 2) working memory, 3) response-inhibition and 4) while dialing a phone.
- COMBINE assessments were blinded to participants' imaging and vice versa.

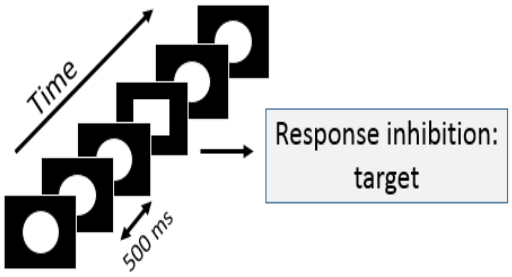


METHODS: Cognitive tasks: Regular & the COMBINE

- Cognitive tasks performed while standing and while walking:
  - Motor sequencing: Luria Motor Sequences task
  - Working Memory: 2-back verbal paradigm
  - Response inhibition: Go- No go task
  - cellphone dialing task: an ecologically valid task
- Instructions included task accuracy and RT.
- COMBINE: did not dictate any task prioritization.
- Order of tasks was randomized.



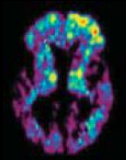
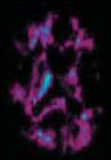




METHODS: PET imaging

- Fibrillar Aβ burden:
  - [11C]PiB (15 mCi)
  - 30 min PiB-PET study (6x300 sec frames)
  - Acquisition: 40-70 min post-injection.
- High-Aβ (PiB(+)) and low-Aβ (PiB(-)) groups, defined on standardized PiB SUVR cutoffs of global six regions of interest.

RESULTS: Sample Characteristics

	Whole group N=28	 PiB (+) N=16	 PiB (-) N=12	p-value for Aβ group differences
Age (yrs)	75.2 ± 5.7	75.9 ± 5.01	74.8 ± 6.6	0.60
Women (n,%)	14 (50%)	8 (50%)	6(55%)	0.58
Education (yrs)	14.7	15 ± 2.8	15.4 ± 2.6	0.74
BMI (kg/m^2)	26.4 ± 4.2	27 ± 3.8	25 ± 5.0	0.33
Comorbidity Index	3.0 ± 1.4	3.1 ± 1.4	2.7 ± 1.4	0.41
MOCA	26.2 ± 2.5	26.5 ± 2.5	25.9 ± 2.6	0.59
DSST	54 ± 13	51.7 ± 12.2	59 ± 14	0.24
SPPB	11 ± 1.5	10.2 ± 1.7	11.4 ± 1.1	0.08
Grip Strength (cm^2)	50.2 ± 18	35.6 ± 18.4	37.4 ± 15.6	0.69
UPDRS	2.6 ± 2.4	3.7 ± 2.8	3.4 ± 2.1	0.70

MOCA: Montreal Cognitive Assessment; **DSST**: Digit Symbol Substitution Test; **SPPB**: Short Physical Performance Battery; **UPDRS**: Unified Parkinson's Disease Rating Scale

PiB Group Differences in Gait Speed (m/sec) across Walking Conditions.

	PiB (+)	PiB (-)	p-value
Regular Walk (without concurrent task)	1.14 ± 0.16	1.16 ± 0.21	0.75
Response inhibition (Go No-go task)	0.94 ± 0.25	1.11 ± 0.26	0.08
Working memory (2-back task)	0.88 ± 0.22	1.04 ± 0.25	0.11
Simple Motor sequencing (Open & close hands)	1.03 ± 0.22	1.3 ± 0.9	0.012
Complex Motor Sequencing (Luria Motor Task)	0.75 ± 0.24	0.98 ± 0.15	0.027
Dialing a phone	0.74 ± 0.19	0.89 ± 0.20	0.06

CONCLUSIONS:

- The COMBINE is related to dynamic changes in the aging brain.
- Amyloid burden is associated with slower gait speed during multitasking.
- Amyloidosis may play an important role in deficits in the COMBINE.
- Tasks of COMBINE could serve as “stress-test” of the brain used to pre-screen vulnerable older adults for clinical amyloid imaging.
- The relationship between the COMBINE and glucose metabolism remains unclear.

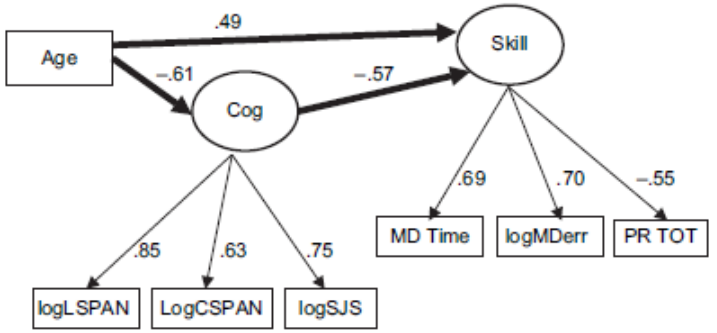
Motor Learning and Aging

Evidence in Aging

(most data is in healthy young and in clinical or rehab populations)

- Motor skill acquisition is slower in older people
- Motor skill acquisition is affected by working memory in older adults

FIGURE 3. Model 3 is a test for partial mediation of age-related skill learning performance differences by cognitive resources. Age has a significant negative direct effect on both the cognitive factor and the skill learning factor and there is significant mediation of age-related effects on skill learning by the cognitive resources factor. This model demonstrates the best fit of the group, indicating that partial mediation structure describes these data very well.



Kennedy KM 2008

Rationale for BLSA Projects in Development

- Most studies to date are cross sectional whereas BLSA can develop longitudinal data
- BLSA can begin to identify the earliest changes that lead to subsequent poor performance
- BLSA can link to cutting-edge imaging
- BLSA can link to biomarker development

BLSA Gait lab project

Energy cost and smoothness

(with Woie-Nan Bair and J Meusch)

Aims

1. What is the best way to assess smoothness?
2. Does smoothness contribute to energy efficiency of movement?
3. Do changes in smoothness across walking conditions affect energy efficiency?
4. What is the role of the CNS in smoothness and efficiency?

Methods

1. Smoothness data acquired from accelerometer and COM from motion analysis
2. Processed using Harmonic Ratios and newer methods such as Normalized Jerk Cost
3. Evaluate associations between smoothness and efficiency under multiple walking conditions (normal, fast, dual task, narrow)
4. Examine influence of brain structure and cognition on these relationships

BDNF pilot: Rationale

with M Mattson, S Resnick, J Mattison, D Kapogiannis, T Tanaka, L Ferrucci

- BDNF acts through its receptor trkB to promote neuronal health, synaptic plasticity, NMJ and long term potentiation
- Studies of peripheral blood BDNF level associations with cognition, movement, learning, exercise and aging have been mixed.
- Recently the precursor proBDNF has been found to have effects antagonistic to BDNF, especially by inhibiting potentiation and promoting apoptosis.
- A short form of trkB (truncated trKB)binds to and inhibits BDNF function.
- Only recently have assays been able to distinguish BDNF from proBDNF
- A BDNF polymorphism VAl66Met alters the ratio of proBDNF to BDNF and has been variably associated with indicators of synaptic plasticity.

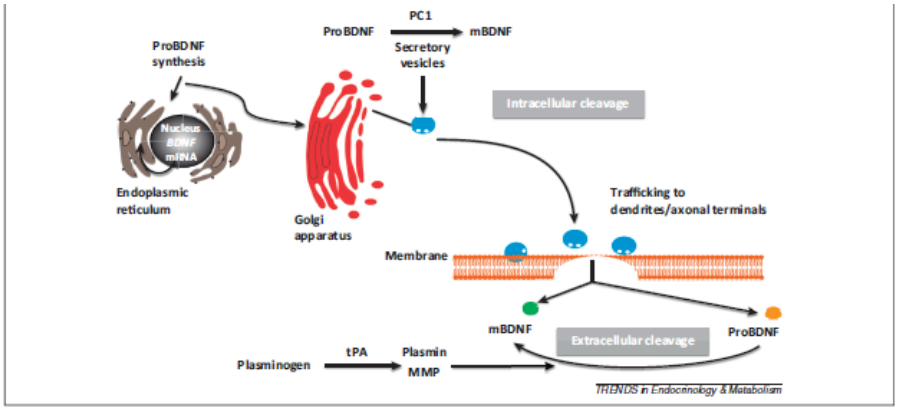


Figure 1. Mechanisms for the production and release of brain-derived neurotrophic factor (BDNF). BDNF mRNA is translated into proBDNF protein in the endoplasmic reticulum. ProBDNF is transported into the Golgi and processed to the mature form of BDNF (mBDNF) by extracellular protein convertase 1 (PC1) within the vesicles. The secretory granules are trafficked to the sites of release in the axonal or dendritic terminals. Neurons secrete both proBDNF and mBDNF in an activity-dependent manner. The tissue-type plasminogen activator (tPA) forms mBDNF by activating a plasminogen, which then cleaves the precursor molecule. Alternatively, extracellular metalloproteinases (MMP) process proBDNF to generate mBDNF.

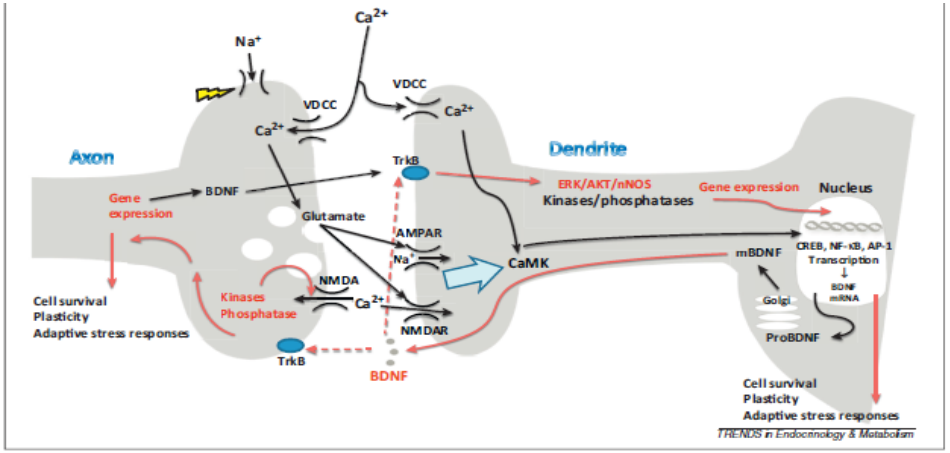


Figure 2. Biological actions of BDNF. When an axon potential reaches the presynaptic terminal of an axon, Na^+ influx depolarizes the plasma membrane, and this triggers Ca^{2+} influx and release of the excitatory neurotransmitter glutamate into the synaptic cleft. Glutamate binds to AMPA and NMDA receptors at the postsynaptic membrane. Activation of the AMPA receptors results in membrane depolarization and Ca^{2+} influx via NMDA and VDCC. Ca^{2+} engages CaMKs that activates CREB and NF-κB which in turn induce the transcription of the *Bdnf* gene. mBDNF is released at synapses and activates TrkB receptors, resulting in activation of downstream signaling cascades including PLCγ, PI3K and MAPKs and subsequent expression of genes crucial for the survival and plasticity of neurons. BDNF signaling also elicits rapid effects on membrane excitability and synaptic transmission via altering the activation kinetics of NMDA receptors and increasing the number of docked synaptic vesicles in the presynaptic terminal. Abbreviations: AMPA(R), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (receptor); BDNF, brain-derived neurotrophic factor; CaMK, Ca^{2+}/calmodulin-dependent kinase; CREB, cAMP response element-binding protein; MAPK, mitogen-activated protein kinase; mBDNF, mature form of BDNF; NF-κB, nuclear factor κB; NMDA(R), *N*-methyl-D-aspartate (receptor); PI3K, phosphatidylinositol 3-kinase; PLCγ; phospholipase Cγ; VDCC, voltage-dependent Ca^{2+} channel.

Marosi and Mattson 2014

BDNF pilot: AIMS

- Assess agreement among circulating and CSF levels of three signaling molecules (BDNF, proBDNF and truncated trkB) in ongoing clinical trials at the NIA Clinical Research Core.
- In BLSA, assess the effect of the Val66Met polymorphism on circulating levels of the three molecules
- In BLSA, evaluate potential relationships among the three molecules and the polymorphism against neurological and muscle function as well as gait and cognition.
- In the 25 year NIA primate trial of caloric restriction, compare levels and relationships among the three molecules.

fMRI of motor learning and reaction time variability (with D Reiter, S Resnick, Teresa Tian et al)

AIMS

1. Integrate studies of motor learning and variability into neuroimaging at BLSA

2. Refine protocol for studying the effect of age and brain health on regional activation patterns during simple and complex reaction time tasks and motor sequence learning.

3. Relate these findings to BLSA data on fitness, gait lab, cognition and neurological examination

Summary

- Thinking and Moving are intimately related, affected by aging, are major sources of late life disability and may share underlying causal processes
- The intramural program at NIA can identify collaborative efforts to study the shared causes of age-related changes in cognition and movement