Gait and Cognition:
Cause, Effect, Both or Neither

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Gait and Brain Talk October 15, 2018
Objectives

• To present the impact of gait changes in aging
• To present evidence for the relationship between gait and cognition
• To discuss links between gait and cognition
• To discuss interventions in gait and cognition
Case

• A 62 year old woman was noted to be anxious and intermittently forgetful by her husband
  – Her GP started an antidepressant
• She was able to take care of herself, though occasionally forgot appointments
• She had a MoCa score of 26/30
  – Points lost for clock drawing, letter fluency and memory
• She had a normal neurological examination
  – Except that she slowed down and had to pause while walking and listing animal names out loud
Fig. 1. Model of gait proposed by Lord et al. (2013) for older adults. Domains include: pace, rhythm, variability, asymmetry and postural control.

Rosie Morris, Sue Lord, Jennifer Bunce, David Burn, Lynn Rochester

Gait and cognition: Mapping the global and discrete relationships in ageing and neurodegenerative disease

Neuroscience & Biobehavioral Reviews, Volume 64, 2016, 326–345
http://dx.doi.org/10.1016/j.neubiorev.2016.02.012

Morris R Neurosci Biobehav Rev 2016
Vergheze J JNNP 2007
Hollman JH Gait Posture 2011
Verlinden VJ 2013
Lord S J Gerontol 2013
Causality (Bradford Hill’s Guidelines)

• Strength of association
• Consistency
• Specificity
• Temporality
• Biological gradient
• Plausibility
• Coherence
• Analogy
• Experiment

AB Hill Proc Royal Soc Med 1965
Strength of Association: Reserve

Callisaya ML, Geroscience 2017
Consistency

- Quantitative studies of gait
  - Across cognitive measures
    - Global
    - Executive function
    - Memory
    - Processing speed
- ES 0.11-0.17 (N Demnitz 2016)
- 1.2-1.4 m/s (NM Peel, 2018):
  - - 0.11 m/s CI
  - - 0.22 m/s mild dementia
  - - 0.41 m/s in moderate dementia
Cross-Sectional and Longitudinal Association (Morris)

Morris R Neurosci Biobehav Rev 2016
Quan M J Gerontology 2017
Temporal Sequence: Gait Preceding

- 52-2776 participants with 2-9 year follow up
  - Gait speed in majority
    - MMSE, memory, EF, processing speed, visuospatial function (8)
    - Change in state to MCI or dementia (14)
- Slow gait associated with decline
  - Short step length associated with cognitive decline
  - Rhythm associated with memory; abnormal pace with EF
- Gait speed associated with the risk of significant cognitive decline, dementia, Alzheimer disease
  - Poor rhythm or variability associated with dementia
  - Impaired pace associated with vascular dementia

Kikkert LE Ageing Res Rev 2016
Hooghiemstra AM, J Geront 2017
Gait Impairment Precedes Cognitive Decline in Parkinson’s Disease

Research Article

Gait Rather Than Cognition Predicts Decline in Specific Cognitive Domains in Early Parkinson’s Disease

Rosie Morris, Sue Lord, Rachael A. Lawson, Shirley Coleman, Brook Galna, Gordon W. Duncan, Tien K. Khoo, Alison J. Yarnall, David J. Burn, and Lynn Rochester

1Institute of Neuroscience, 2Newcastle Institute for Ageing, 3UK and Industrial Statistics Research Unit, and 4School of Biomedical Sciences, Newcastle University, Newcastle upon Tyne, UK. 5Centre for Clinical Brain Science, University of Edinburgh, UK. 6School of Medicine and Menzies Health Institute Queensland, Griffith University, Australia. 7School of Medicine, University of Wollongong, New South Wales, Australia
Cognitive Impairment Preceding Gait

- Less consistent evidence (Clouston SAP, 2013)
- Longitudinal study of 5888 people
  - DSST associated with decline in cognition (3MS), less on mood (CES-D) and gait (speed)
    - Defined cutoffs for “clinical disorder”
      - $<80$ vs $>85$ for cognition
      - $>10$ vs $<5$ for mood
      - $<0.6$ m/s vs $>1$ m/s for gait

Rosano C, Age Ageing 2016
Digit Symbol Substitution Test

```
<table>
<thead>
<tr>
<th>DIGIT</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
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<tbody>
<tr>
<td>SYMBOL</td>
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<td>ılı</td>
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<td>0</td>
<td>a</td>
<td>x</td>
<td>=</td>
<td></td>
</tr>
</tbody>
</table>

SAMPLES

2 1 3 7 2 4 8 1 5 4 2 1 3 2 1 4 2 3 5 2 3 1 4 6 3

1 5 4 2 7 6 3 5 7 2 8 5 4 6 3 7 2 8 1 9 5 8 4 7 3

6 2 5 1 9 2 8 3 7 4 6 5 9 4 8 3 7 2 6 1 5 4 6 3 7

9 2 8 1 7 9 4 6 8 5 9 7 1 8 5 2 9 4 8 6 3 7 9 8 6

Score: [Blank]

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Health ABC Study Form
From: Digit Symbol Substitution test and future clinical and subclinical disorders of cognition, mobility and mood in older adults
Age Ageing | © The Author 2016. Published by Oxford University Press on behalf of the British Geriatrics Society. All rights reserved. For Permissions, please email: journals.permissions@oup.com
Victoria Longitudinal Study (VLS): Design, Sample, and Measures

- VLS Sample 1 (1986)
- VLS Sample 2 (1993)
- VLS Sample 3 (2001)

- Wave 1 (W1) (1986)
- W2 (1989)
- W3 (1992)
- W5 (1998)
- W6 (2002)
- W7 (2005)
- W8 (2010)

- Cog. Assess.
- Cog. Assess.
- Cog. Assess.
- Cog. Assess.
- Cog. Assess.
- Cog. Assess.
- Cog. Assess.
- Gait

- Sample 1, Waves 1-8 (n=32)
Gait Assessment

16’ GAITRite Computerized Walkway

- Embedded pressure sensors enable capture of footfalls over time
- Yields nuanced measurements of various facets of gait/walking
  - **Spatial** (step length and width)
  - **Temporal** (gait velocity, stance time)
  - **Variable** (stride time variability)
- 4 passes of mat for each of **two conditions**: walk only + dual task
Trajectories of 25-Year Cognitive Change
Moderating Influence of Gait

**FIGURE 2** Moderating effect of normalized gait velocity on age-related cognitive change. For each cognitive outcome, age-related change is plotted as a function of average (grand mean at wave 8), slower than average (1 SD slower than the grand mean at wave 8), and faster than average (1 SD faster than the grand mean at wave 8) normalized gait velocity. (A) Digit symbol substitution: number correct. (B) Word recall. (C) Digit symbol substitution: incidental recall. (D) Vocabulary.
Does It Go Both Ways?

• Tian Q et al. Age Ageing 2017
  – Significant bidirectional association cognition
    • Gait associated with DSST and TMT-B decline
      – DSST and TMT-B with gait decline
    • Fast gait associated with DSST and TMT-B and CVLT decline

• Best JR et al. J Gerontol A 2016
  – Self selected gait speed (6 meters) predicts DSST decline
  – Cognitive decline didn’t predict gait decline

• Qualls C et al. J Nutr Health Aging 2017
  – Age (above or below 78 years) affected risk of transition
    • People improved, but less likely to if ApoE4+ or poor health
      – Low BMI increased chance in younger, but opposite in older
      – No clear temporal relationship between cognition and gait speed
Transitions

Qualls C JNHA 2017
Biological Gradient

• In **cognitively intact**, motor function is associated with increased dementia risk
  – **Global scores, balance and gait**
    • HR: 1.94; 95% CI: 1.41, 2.65
  – **Dose response** (Quan M, 2017)
    • HR: 1.13 with each 1 dm/s decrease in speed

• Risk increased with **cognitive complaints** (MCR) or **cognitive impairment** (MCI)
  – Variability, dual task, walking speed reserve, long walks

Kueper JK Age Ageing 2017; Valkanova V Gait Posture 2017; Stijntjes M J Geront 2017; Savica R JAD 2017
Figure 2 MCR and risk of incident cognitive impairment (A) and dementia (B) Kaplan-Meier survival curves with 95% confidence interval over 12 years’ follow-up in pooled samples.
Dual Task and Dementia Risk

• Gait speed is associated with cognitive decline in many studies, but not all (AD, LBD, VaD)
  • Associated with MCI (Verghese J, 2007, 2008)
    – Pace variables associated with naMCI
    – Rhythm and variability with aMCI

• Variability more sensitive (Beauchet O, 2014)

• Dual-task and dementia (Montero-Odasso M 2017)

Brenowitz W; Bahureska L Gerontology 2017
Figure Legend:

Cumulative Hazard Ratio for Progression to Dementia for Low and High Dual-Task Cost in Gait Velocity (n = 112) A, Dual-task gait cost (DTC) while counting backward. B, While performing serial sevens subtractions. C, While naming animals.
Plausibility: Common Pathology?

• Age/disease-associated pathologies and gait
  – White matter
    • High signal (Callisaya ML 2013; de Laat 2010; Silbert LC, 2008; LADIS; Nadkarni NK; but see Mergeche JL 2016; Valankova V 2018)
    • Diffusion (Tian Q 2014, 2015; Rosario BL 2016; Seiler S 2017; Ghantavati T 2018)
  – Grey matter
    • Cortical (de Laat KF 2011,12; Callisaya ML 2013; Rosano C 2012,14,15; Kim YJ 2016) and Subcortical (Demnitz N 2017)
      – Cerebrovascular (Wang N, 2016; Smith EE, 2015)
    • Functional (Holtzer R, 2014; Hamacher D, 2015; Reijmer YD, 2015)
    • Microbleeds (de Laat KF 2011; Stijnjtes M 2017)
  – Proteinopathy
    • Amyloid (Nadkarni NK 2017; Wennberg AM 2018)
    • ?Tau, ?Synuclein
  – Neurochemistry
    • Dopamine (Noradrenaline) (Metti AL, 2017)
    • Acetylcholine (Pelosin E, 2016; Sarter M, 2014)
White Matter Changes and Gait

Moscofu N 2018

van der Holst HM 2018
Activity Influences Effect of WMD

Fleischman DA 2015
74 year old male with PD

Images acquired on a 3.0 T Siemens PRISMA (Peter S. Allen MR Research Centre, U of A)

**T1 weighted:**
resolution = 1.0 x 1.0 x 1.0 mm
FOV = 256 x 256 x 192 mm
scan duration = 5:21 min

**T2 weighted:**
resolution = 0.5 x 0.5 x 1.0 mm
FOV = 175 x 175 x 70 mm
scan duration = 7:40 min
Figure 2 Mean gait speed by cognitive status over 14 years

Andrea L. Rosso et al. Neurology 2017;89:336-342
Figure 1 Age effects on β-amyloid (Aβ) deposition (A) The effect of age on mean cortical uptake across the lifespan.

Increased PIB binding associated with Cadence and double support time
Temporal lobe binding with velocity
In women all gait parameters associated
In men orbitofrontal binding associated with cadence

Wennberg AM 2018
Fig. 1. Lateral substantia nigra pars compacta (SNc) $R^2*$ change vs change in UPDRS III score. Open circles represent patients who developed freezing of gait (FOG) during the 36 months of clinical follow-up. Squares represent those who did not develop freezing.

Marguerite Wieler, Myrlene Gee, Richard Camicioli, W.R. Wayne Martin

**Freezing of gait in early Parkinson’s disease: Nigral iron content estimated from magnetic resonance imaging**

Journal of the Neurological Sciences, Volume 361, 2016, 87–91

http://dx.doi.org/10.1016/j.jns.2015.12.008
• Broadly inclusive criteria will produce heterogeneous groups that cover the entire dementia population.

• Include almost all co-morbidities and mixed dementias

• Difficult to specify definitions of “pure” disease
## Core Cognitive Battery for Clinical Cohorts

<table>
<thead>
<tr>
<th>Neuropsychological Domain</th>
<th>Tests Used</th>
<th>In other groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropsychological Domain</strong></td>
<td></td>
<td>Tests used</td>
</tr>
<tr>
<td>Memory</td>
<td>WAIS III Vocabulary</td>
<td>=in CIMA-Q</td>
</tr>
<tr>
<td>Memory</td>
<td>RAVLT</td>
<td>=in ONDRI</td>
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<tr>
<td>Memory</td>
<td>Brief Visuospatial Memory test</td>
<td>=in CLSA</td>
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<tr>
<td>Memory</td>
<td>CCNA-CIMA-Q Face-Name Association</td>
<td>=in both CLSA &amp; CIMA-Q</td>
</tr>
<tr>
<td>Memory</td>
<td>Digit Symbol incidental recall</td>
<td>=in both CLSA &amp; CIMA-Q &amp; ONDRI</td>
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<tr>
<td>Memory</td>
<td>Envelope test</td>
<td>=in CIMA-Q</td>
</tr>
<tr>
<td>Executive Function</td>
<td>DKEFS Colour-Word Interference</td>
<td>=in ONDRI</td>
</tr>
<tr>
<td>Executive Function</td>
<td>DKEFS Phonemic Fluency</td>
<td>=in CLSA</td>
</tr>
<tr>
<td>Executive Function</td>
<td>CCNA-CIMA-Q sentence inhibition task</td>
<td>=in both CIMA-Q &amp; ONDRI</td>
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<tr>
<td>Executive Function</td>
<td>Trailmaking</td>
<td>=in both CLSA &amp; ONDRI</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Reaction time test</td>
<td>=in both CLSA &amp; ONDRI</td>
</tr>
<tr>
<td>Language</td>
<td>Animal Fluency</td>
<td>=in CIMA-Q</td>
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<tr>
<td>Language</td>
<td>NACC Language battery</td>
<td>=in ONDRI</td>
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<tr>
<td>Attention/Psychomotor Speed</td>
<td>WAIS-III Digit Symbol-Coding</td>
<td>=in CLSA</td>
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<tr>
<td>Attention/Psychomotor Speed</td>
<td>Digit span F &amp; B</td>
<td>=in both CLSA &amp; CIMA-Q</td>
</tr>
<tr>
<td>General</td>
<td>MoCA</td>
<td>=in both CIMA-Q &amp; ONDRI</td>
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<tr>
<td>Visuoperceptual</td>
<td>Line Orientation</td>
<td>=in CIMA-Q, CIMA-Q, &amp; ONDRI</td>
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<tr>
<td>Visuoperceptual</td>
<td>Object Decision test</td>
<td>=in CIMA-Q, CIMA-Q, &amp; ONDRI</td>
</tr>
<tr>
<td>Visuoperceptual</td>
<td>VOSP letter completion</td>
<td>=in CIMA-Q, CIMA-Q, &amp; ONDRI</td>
</tr>
</tbody>
</table>
Guidelines for Gait Assessments in the Canadian Consortium on Neurodegeneration in Aging (CCNA)

Stephanie Cullen, MSC(C)\textsuperscript{1,*}, Manuel Montero-Odasso, MD, PhD, AGSF, FRCP\textsuperscript{1,2,*}, Louis Bherer, PhD\textsuperscript{3}, Quincy Almeida, PhD\textsuperscript{4}, Sarah Fraser, PhD\textsuperscript{5}, Susan Muir-Hunter, PhD\textsuperscript{1,6}, Karen Li, PhD\textsuperscript{7}, Teresa Liu-Ambrose, PhD\textsuperscript{8}, Chris A. McGibbon, PhD\textsuperscript{9}, William McIlroy, PhD\textsuperscript{10}, Laura E. Middleton, PhD\textsuperscript{10}, Yanina Sarquis-Adamson, PhD\textsuperscript{1}, Olivier Beauchet, MD, PhD\textsuperscript{11}, Bradford J. McFadyen, PhD\textsuperscript{12}, José A. Morais, MD, FRCS\textsuperscript{C} 11, Richard Camicioli, MD, FRCS\textsuperscript{C} 13, The Canadian Gait and Cognition Network\textsuperscript{14}
Variability in Lewy Body Disease

Group Differences in Reaction Time Variability

Average Group Differences in Gait Variability

Courtesy of Kerry Howell, Summer Student
Grey Matter Areas and Gait Variability

Tian Q 2017
UOA9888 64 year old female with FTD
ROI traced using ImageJ
George S, 2011

Subcortical areas associated with Gait

Courtesy of Myrlene Gee
SI Volume Correlates with IIV RT; Thalamic Volume Correlates with CV in Gait

Substantia Inominata Normalized volumes vs SRT_CV: Pearson R = -0.5  p =0.04

Thalamic Normalized volumes vs Swing Time CV: Pearson R = -0.33  p = 0.08
Experiment

• Physical interventions
  – Exercise improves cognitive performance
    • Less clear benefit in dementia
    • MCI studies more consistent (strength, aerobic, balance/stretching)

• Cognitive interventions
  – Less studies

• Combined interventions
  – Consider nutritional factors (Vitamin D, B vitamins, diet)

• Dual task interventions
  – Traditional approaches (Tai Chi)
  – Novel approaches (Tango)

• Animal studies = Coherence
Recent Large Studies

• Look AHEAD (Neurology 2017)
  – Diabetes or overweight
  – 10 years of exercise and dietary intervention
• MAPT (Lancet Neurol 2017)
  – Memory complaints
  – 3 year multi-domain intervention
    • Omega 3 supplementation
• LIFE (JAMA 2015)
  – Sedentary adults
  – Physical activity
• PreDiva (Lancet 2016)
  – At risk adults
  – Multi-domain intervention
• FINGER (Lancet 2015)
  – Cardiovascular (CAIDE) and dementia at-risk
  – 2 year multimodal intervention
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Case Follow Up

• Patient went to Mayo Clinic
• CSF showed “borderline” low A-beta, with minimal change in tau
• Concluded maybe MCI, maybe mild dementia
• Antidepressant stopped
• Patient more anxious since stopping antidepressants, same MoCa
  – Now having more functional deficits – forgot grandchild, can’t do work as an administrator
• Conclusion: mild dementia
Gait and Cognition

- Aging
- Cognition
- Trial
- Degeneration
- Inflammation
- Vascular
- Gait