Standing strong in the roaring 40s – ANZFPS November 18-20 2018

HOBART
Thinking on your feet – the interplay between cognition, gait and falls

Dr Michele Callisaya
Menzies Research Institute Tasmania
Monash Medical Centre, Monash University
The interplay between the cognition, gait & falls

Growing evidence to suggest that the brain and mobility are closely linked well before dementia
Outline

In those without dementia

1. Specific gait patterns associated with falls
2. Specific cognitive domains associated with falls
3. The link between the brain, gait and falls
4. Emerging evidence for novel interventions
Gait and falls

Balance and gait impairments OR 1.9 (95%CI 1.0-3.7)

Gait → Falls

Tinetti M et al NEJM 1988
Gait speed slower than 1.0 m/sec increased the risk of multiple falls

Could other gait measures be important

Callisaya ML et al Age and Ageing 40 2011
Poorer gait performance with advancing age

<table>
<thead>
<tr>
<th>Preferred and fast speed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spatial</strong></td>
</tr>
<tr>
<td>Step length</td>
</tr>
<tr>
<td>Step width</td>
</tr>
</tbody>
</table>

Walk ratio = step length/cadence
Intra-individual gait variability is higher with advancing age

Walking is normally a highly consistent activity

- Fluctuation in a gait parameter from one step to the next = intra-individual gait variability
- More sensitive predictor of falls risk?
- Under less conscious control

Step length, step time, step width, double support phase

Callisaya ML et al Age and Ageing 2010
Gait patterns and risk of multiple falls

- Step length variability: RR 2.01 95%CI 1.07, 3.80
- Double support phase variability: RR 2.08 95%CI 1.06, 4.08
- Walk ratio (shorter steps, faster cadence): RR 0.73 95% CI 0.63, 0.85
Cognitive and falls

- Cognitive impairment OR 5.0 (1.80, 13.70)\(^1\)
- Global cognitive impairment (MMSE<26): OR 2.13 (1.56, 2.90)\(^2\)
- MCI vs no MCI: OR 1.72 (1.03–2.89)\(^3\)

\(^1\) Tinetti M NEJM 1988
\(^2\) Muir S et al Age and Ageing 2012
\(^3\) Delbaere K et al Am J Geri Psych 2012
Which cognitive domains are associated with increased risk of falls?
Cognition and falls risk

Executive function/attention

- Victoria Stroop
  - Car
  - Hat
  - Red
  - Blue
  - Bed
  - Yellow
- Controlled Oral Word Association Test

Visualspatial ability

- Rey Complex Figure

Processing speed

- Digit symbol coding
  - 1 2 3 4 5 6 7 8 9
- Symbol search

Memory

- Hopkins Verbal Learning Test
  - Immediate
  - Delay
  - Recognition
- Rey Complex Figure - Delayed Reproduction (20 min)

Martin K et al ..Callisaya ML J Gerontology Med Sci 2013
Interplay between cognition, gait and falls

- Gait speed and gait patterns
- Specific cognitive domains
- Falls
Gait may provide a window into the brain

Are there different signatures of gait underpinned by specific cognitive and brain impairments
Dual-task

For one task (eg walking speed):

• Dual task cost (DTC)

\[
\text{DTC} = \frac{\text{Dual} - \text{Single}}{\text{Single}}
\]

Those with greater cognitive impairment have greater dual-task cost

Muir S et al  Gait and Posture 2012
Gait initiation time is associated with the risk of multiple falls—A population-based study

<table>
<thead>
<tr>
<th>Gait initiation time</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single task</td>
<td>1.28</td>
<td>1.03, 1.58</td>
</tr>
<tr>
<td>Dual task</td>
<td>1.14</td>
<td>1.02, 1.27</td>
</tr>
</tbody>
</table>

![Diagram of gait phases](image)
Single and dual task gait are equivalent in predicting falls risk

- Single and dual task were equivalent in predicting falls
- No change in subgroups (e.g. slow vs fast walkers)
- Types of secondary cognitive tasks not important

What can gait tell us about cognitive and brain impairments
## Cognitive Function, Gait, and Gait Variability in Older People: A Population-Based Study

Kara L. Martin, Leigh Blizzard, Amanda G. Wood, Velandai Srikanth, Russell Thomson, Lauren M. Sanders, and Michele L. Callisaya

### Multivariable linear regressions between cognition and gait measures

<table>
<thead>
<tr>
<th></th>
<th>Regression Coefficient (β), 95% Confidence Interval</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Gait</td>
<td>Processing speed</td>
<td>Executive function</td>
</tr>
<tr>
<td>Gait speed (cm/s⁻¹)</td>
<td></td>
<td>2.42 (0.78, 4.06)†</td>
<td>-1.57 (−2.67,−0.47)‡</td>
<td>0.28 (-0.16,0.71)</td>
</tr>
<tr>
<td>Step time (ms)</td>
<td></td>
<td>-4.95 (−9.36,−0.55)‡</td>
<td>2.57 (−0.41,5.55)</td>
<td>-0.08 (-1.25,1.08)</td>
</tr>
<tr>
<td>Step length (cm)</td>
<td></td>
<td>0.82 (0.16,1.47)‡</td>
<td>−0.60 (−1.04,−0.16)†</td>
<td>0.16 (0.01,0.33)</td>
</tr>
<tr>
<td>Support base (cm)</td>
<td></td>
<td>-0.27 (−0.52,−0.29)‡</td>
<td>0.14 (−0.03,0.30)</td>
<td>-0.04 (-0.10,0.03)</td>
</tr>
<tr>
<td>DSP (%)</td>
<td></td>
<td>-0.31 (−0.62,−0.004)‡</td>
<td>0.25 (0.05,0.46)‡</td>
<td>-0.02 (-0.07,0.10)</td>
</tr>
<tr>
<td>Gait variability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step time (ms)</td>
<td></td>
<td>-0.69 (−1.78,0.40)</td>
<td>0.78 (0.05,1.51)‡</td>
<td>-0.28 (-0.56, 0.001)</td>
</tr>
<tr>
<td>Step length (cm)</td>
<td></td>
<td>-0.04 (−0.12,0.04)</td>
<td>0.004 (−0.05,0.05)</td>
<td>-0.01 (-0.01,0.01)</td>
</tr>
<tr>
<td>Support base (cm)</td>
<td></td>
<td>-0.04 (−0.10,0.02)</td>
<td>0.03 (−0.01,0.07)</td>
<td>-0.004 (-0.02,0.01)</td>
</tr>
<tr>
<td>DSP (ms)</td>
<td></td>
<td>-1.13 (−2.10,−0.15)‡</td>
<td>0.78 (0.13,1.44)‡</td>
<td>-0.34 (-0.60,-0.09)‡</td>
</tr>
</tbody>
</table>

Morris R. Neuroscience and Biobehavioural Reviews 2016
Cognition and gait - Summary so far…

• Executive function and processing speed most consistently associated with gait speed (and step length) and DSP variability

• Addition of visual-spatial ability with DSP variability

• Memory not associated any of the gait measures
Are there common underlying impairments in brain structure?

Common neural mechanisms that might be targeted by interventions

- Executive function
- Processing speed
- Visuospatial function

- Gait and gait variability

- Falls
Possible underlying mechanisms of cognition, gait and falls

Cerebral small vessel disease

Subcortical Infarcts
White matter hyperintensities (WMH)
Microbleeds

Healthy brain
Atrophic brain
WMH are associated with cognition (EF and processing speed), gait, gait variability and falls.
Bilateral frontal and periventricular WMH are associated with poorer gait

Srikanth V et al Annals Neurology 2010
Debette S BMJ 2010
Subcortical infarct are associated with cognition (EF and processing speed), gait and falls

<table>
<thead>
<tr>
<th>TASCOG and MAS</th>
<th>Multiple falls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subcortical infarcts</strong></td>
<td>RR</td>
</tr>
<tr>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>1.15</td>
</tr>
<tr>
<td>2</td>
<td>1.15</td>
</tr>
<tr>
<td>≥3</td>
<td>1.89</td>
</tr>
</tbody>
</table>

Choi P….V.K Srikanth Stroke 2012
Callisaya ML…K. Delbaere International journal of stroke 2014
Disruption of frontal-subcortical circuits

- **Motor circuit**
  - Primary motor, SMA, premotor
  - Putamen
  - Globus pallidus
  - Thalamus

- **Cognitive**
  - Dorsolateral prefrontal
  - Caudate
  - Globus pallidus
  - Thalamus

- **Apathy**
  - Medial frontal
  - Nucleus accumbens
  - Globus pallidus
  - Thalamus

- **Disinhibition**
  - Orbital frontal
  - Caudate
  - Globus pallidus
  - Thalamus

Figure adapted from Bonelli R Translational Research 2007
Brain atrophy in multiple areas is associated with gait speed (step length)

**Attention/cognitive control**
- prefrontal, insula, temporal lobe, subcortical nuclei, limbic

**Gait initiation and regulation**
- basal ganglia, Supplementary motor area (SMA)

**Execution**
- premotor, SMA

**Sensory**
- parietal, precuneus, thalamus, occipital, cuneus

**Balance**
- cerebellum

Consistent with the notion that gait requires the complex interaction of distributed brain cortical networks

Callisaya ML ….Srikanth VL PLOS ONE 2014
Relationship of regional brain β-amyloid to gait speed

Natalia del Campo, PhD
Pierre Payoux, MD, PhD
Adel Djilali, PhD
Julien Delrieu, MD
Emiel O. Hoogendijk, PhD
Yves Rolland, MD, PhD
Matteo Cesari, MD, PhD
Michael W. Weiner, MD, PhD
Sandrine Andrieu, MD, PhD
Bruno Vellas, MD, PhD
For the MAPT/DSA Study Group

Correspondence to
Dr. del Campo:
nata.delcampo@gmail.com

ABSTRACT

Objective: To investigate in vivo the relationship of regional brain β-amyloid (Aβ) to gait speed in a group of elderly individuals at high risk for dementia.

Methods: Cross-sectional associations between brain Aβ as measured with [18F]florbetapir PET and gait speed were examined in 128 elderly participants. Subjects ranged from healthy to mildly cognitively impaired enrolled in the control arm of the multidomain intervention in the Multidomain Alzheimer Preventive Trial (MAPT). Nearly all participants presented spontaneous memory complaints. Regional [18F]florbetapir (AV45) standardized uptake volume ratios were obtained via semiautomated quantitative analysis using the cerebellum as reference region. Gait speed was measured by timing participants while they walked 4 meters. Associations were explored with linear regression, correcting for age, sex, education, body mass index (BMI), and APOE genotype.

Results: We found a significant association between Aβ in the posterior and anterior putamen, occipital cortex, precuneus, and anterior cingulate and slow gait speed (all corrected p < 0.05). A multivariate model emphasized the locations of the posterior putamen and the precuneus. Aβ burden explained up to 9% of the variance in gait speed, and significantly improved regression models already containing demographic variables, BMI, and APOE status.

Conclusions: The present PET study confirms, in vivo, previous postmortem evidence showing an association between Alzheimer disease (AD) pathology and gait speed, and provides additional evidence on potential regional effects of brain Aβ on motor function. More research is needed to elucidate the neural mechanisms underlying these regional associations, which may involve motor and sensorimotor circuits hitherto largely neglected in the pathophysiology of AD.

Neurology® 2016;86:36-43
What scope do we have for intervention?
Interventions targeting vascular risk factors?

Exercise?

Diet?

Blood pressure?

Pahor M et al JAMA LIFE study 2014
Sink K JAMA Life Study 2015
Milaneschi Y Exp Gerontol 2011
Valles-Pedret C et al JAMA int Med 2015
Interventions

Drugs

• Acetylcholinesterase inhibitors e.g donepezil\textsuperscript{1,2}
• NMDA receptor antagonists eg Memantine\textsuperscript{2}
• Methylphenidate\textsuperscript{3}

Non-invasive electrical stimulation

• Improves executive function and working memory
• Improves dual-task cost\textsuperscript{4}

\textsuperscript{1}Monterro-Odasso M et al JAD 2015
\textsuperscript{2}Beauchet O Drug Aging 2014
\textsuperscript{3}Ben-Itzhak R JAGS 2008
\textsuperscript{4}Manor B et al J Cogn Neurosci 2016
Cognitive training

>70, walked at less than 1 m/s, sedentary n=24
45-60min x3 week for 8 weeks (seated) vs waitlist

‘Mindfit’ program

Interactive cognitive-motor step training

Fig 2. Screenshots of game screens.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0145161
Virtual reality training on a treadmill

42% reduction in falls after 6 months compared to treadmill alone

Past history 2 or more falls
6 weeks (x 3 week) training

Mirelman A et al Lancet 2016
Conclusion

• Gait and cognition should not be considered separately in relation to falls risk

• Neurodegeneration and cerebral small vessel disease in areas important for cognition (executive fx, processing speed) and motor control

• There is emerging evidence from clinical trials that addressing cognition may also improve gait and reduce falls risk
Thank you
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See you in HOBART

Credit: Tourism Tasmania and Garry Moore