Impaired sensorimotor processing during complex gait precedes behavioral changes in middle-aged adults

Trina Mitchell[1,2], Faryn Starrs, MSc[1,2], Jean Paul Soucy, MD, MSc[3,4], Alexander Thiel, MD, PhD[3, 5], & Caroline Paquette*, PhD[1,2]

[1] Department of Kinesiology and Physical Education, McGill University, Montréal, Quebec, Canada
[2] Centre for Interdisciplinary Research in Rehabilitation, Montréal, Quebec, Canada
[3] Department of Neurology and Neurosurgery, McGill University, Montréal, Quebec, Canada
[4] PERFORM Centre, Concordia University, Montréal, Quebec, Canada
[5] Jewish General Hospital, Lady Davis Institute for Medical Research, Montréal, Quebec, Canada

*** Corresponding Author:** caroline.paquette@mcgill.ca; Department of Kinesiology and Physical Education, McGill University, 475 Avenue Des Pins Ouest, H2W 1S4; 514-398-4184 x00890

Abstract

Gait impairment during complex walking in older adults is thought to result from a progressive failure to compensate for deteriorating peripheral inputs by central neural processes. It is the primary hypothesis of this paper that failure of higher cerebral adaptations may already be present in middle-aged adults who do not present observable gait impairments. We therefore compared metabolic brain activity during steering of gait (i.e., complex locomotion) and straight walking (i.e., simple locomotion) in young and middle-aged individuals. Cerebral distribution of [^{18}F]-fluorodeoxyglucose, a marker of brain synaptic activity, was assessed during over ground straight walking and steering of gait using positron emission tomography in seven young adults (aged 24±3) and seven middle-aged adults (aged 59±3). Brain regions involved in steering of gait (posterior parietal cortex, superior frontal gyrus, and cerebellum) are retained in middle-age. However, despite similar walking performance, there are age-related differences in the distribution of [^{18}F]-FDG during steering: middle-aged adults have (i) increased activation of precentral and fusiform gyri, (ii) reduced deactivation of multisensory cortices (inferior frontal, postcentral, fusiform gyri), and (iii) reduced activation of the middle frontal gyrus and cuneus. Our results suggest that pre-clinical decline in central sensorimotor processing in middle-age is observable during complex walking.

Key Words: Complex gait, Positron emission tomography, Cerebral glucose metabolism, Behavior, Middle age

Introduction

Gait disturbances significantly contribute to an increased risk for falls in the elderly (1). This problem arises especially during challenging walking conditions such as dual-tasking or changing the gait trajectory to steer around obstacles (i.e., steering of gait) (2, 3). Indeed, steering of gait requires integration of complex sensory information from multiple sources (visual, vestibular, proprioceptive), motor planning, and asymmetric motor output for the legs to cover different distances while maintaining the same timing (4). Moreover, gait impairment under complex walking conditions is associated with cognitive and sensorimotor deficits and is typically observed after middle-age (45-65) (1, 2, 5).

In general, locomotor control is organized hierarchically in the central nervous system such that locomotor patterns produced by spinal pattern generators are largely regulated by basal ganglia and brainstem nuclei for *simple locomotion* (i.e., straight walking) (6). These neural processes for locomotion depend on normal peripheral sensory and proprioceptive afferent inputs and successful integration of this information in central circuits integrating higher-level cerebral structures (i.e., primary motor cortex, premotor area, prefrontal cortex, posterior parietal cortex) with the basal ganglia nuclei, thalamus, cerebellum, and subcortical nuclei (i.e., subthalamic and mesencephalic locomotor nuclei) responsible for output to spinal pattern generators (6, 7). Importantly, this higher-level control is thought to have a limited role in simple locomotion, as shown by experiments in decorticate cats, which are able to maintain steady-state locomotor patterns despite absent cortical input (8). In contrast, inputs from higher-order frontal and parietal cortical regions are essential for adapting the locomotor pattern to complex situations (9, 10). Thus, complex locomotion is said to be under increased voluntary control compared to steady-state locomotion.

During aging, peripheral proprioceptive systems become impaired and, at the same time, central motor structures show deteriorating function. In a probable attempt at compensation to the degradation of

sensorimotor information, older adults show increased activity of high-level sensorimotor cortical structures (i.e., supplementary motor area, postcentral gyrus, cingulate cortex) during motor tasks (11, 12). Cognitive structures demonstrate similar deterioration, such that there is increased recruitment of cortical regions (i.e., prefrontal and parietal cortices) for executive functions (working memory, visuospatial processing speed, and reasoning) in older adults (13-15). Some of those cognitive domains degenerate as early as middle-age, as demonstrated by increased cortical recruitment that is associated with performance deficits on these tasks in middle-aged subjects (13-15). Importantly, brain regions involved in cognitive control are implicated in age-related gait impairments (16, 17). During gait-related mental imagery tasks, older adults tend to have less deactivation of multisensory (vestibular, visual, somatosensory) cortical regions (18). This is thought to illustrate an aging effect on reciprocal inhibition of sensory information, where older adults tend to co-activate multisensory (i.e., vestibular, somatosensory, auditory) cortical regions instead of prioritizing processing of visual stimuli relevant to the task, a finding that mirrors results from simple visual tasks (19, 20). This poor inhibition of multisensory information processing is believed to result from sensorimotor deficits associated with healthy aging. It is unclear whether neural changes under complex walking conditions precede changes in locomotor performance.

Traditionally, the neural control of locomotion has been measured by functional magnetic resonance imaging (fMRI) during mental imagery of locomotion in subjects constrained to the supine position which can be accommodated by an MR scanner (6, 18, 21, 22). Mental imagery of gait however is only a very poor substitute for actual upright locomotion, in particular because changing peripheral sensory and proprioceptive inputs are absent during imagined locomotion while networks involved in primary motor and somatosensory are strongly activated during real locomotion (23) and may be important for control of more complex locomotor activity. In addition, real locomotion engages postural control, known to be under more complex cortical control than simple locomotor output alone (24). Compared to forward walking, complex upright walking (e.g., negotiating a trajectory around obstacles)

has been shown to require increased frontal lobe activity, which is even more apparent in older than young adults (16).

More recently, there has been growing interest in measuring whole-brain regional cerebral glucose metabolism (regional cerebral metabolic rate for glucose, rCMRGluc) of [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) using Positron Emission Tomography (PET), a proxy for brain activity, during unconstrained motor tasks (25-28). These paradigms are unique in that they allow for measurement of whole-brain activity during actual upright locomotor tasks; however, they have not yet been used to understand the neural mechanisms underlying complex locomotion.

Middle-aged adults may already have central control impairments during complex walking related to the aforementioned age-related cognitive and sensorimotor decline. Therefore, we sought to determine if neural activity for over ground steering of gait, relative to straight walking, is different in middle-age as compared to what takes place in young subjects. Control for steering of gait is expected to be preserved in middle-aged adults and is hypothesized to require increased activation of brain regions involved in cognitive control (i.e., parietal and prefrontal cortices) compared to straight walking. Furthermore, it is hypothesized that middle-aged adults will have increased activation of brain regions for cognitive control, and reduced deactivation of multisensory cortical regions compared to young adults.

Methods

Subjects

Seven young adults (3 males, aged between: 20-28, mean age: 24 ± 3) and seven middle-aged adults (4 males, aged between: 55-63, mean age: 59 ± 2), free from overt general cognitive impairment (Montreal Cognitive Assessment >26), were included in the present study. All subjects were right-hand dominant as determined by the Edinburgh Handedness Inventory, except for one left-hand dominant

middle-aged adult (29). All subjects had self-report normal or corrected-to-normal vision and reported no difficulty with balance or falls. All participants gave their informed consent in accordance with the Declaration of Helsinki and the project was approved by the McGill Faculty of Medicine Institutional Review Board regulations for human subjects' studies.

Experimental Design

Cerebral glucose metabolism was measured during two locomotor tasks, steering of gait (i.e., complex locomotion) and straight walking (i.e., simple locomotor reference task) using PET imaging with [^{18}F]-FDG. Each task was performed continuously for 40 minutes immediately following a 185 MBq bolus injection of [^{18}F]-FDG. Tasks were randomized across sessions and completed at least 48 hours apart to avoid spillover effects. All subjects were non-diabetic and fasted overnight prior to the acquisition to ensure optimal cerebral FDG uptake (30). Importantly, straight walking served as the reference task to isolate activations associated with steering of gait, accounting for upright posture and simple locomotor output. Following the gait tasks, participants walked to the PET imaging suite, which took approximately 5-minutes for all subjects. Thus, PET imaging occurred 50 minutes post-injection.

For the walking tasks, four lanes (1.2 m width by 28 m length) were delineated by yellow and orange cones in a 6 m by 34 m room (**Figure 1**). In the straight walking task, participants were instructed to walk in the middle of the lane, making 180 degree turns (~40 turns for the 40-minute walking protocol) into the next lane. An identical placement of cone markers was used in the steering task. For steering, participants were instructed to continuously turn around the yellow cones, placed in an order that ensured participants had to constantly adjust their walking trajectory in an unpredictable manner. The same trajectory was used across subjects and all subjects were instructed to walk at their self-selected walking speed. All participants wore a safety harness and a research assistant followed them to prevent a fall (31). None of the participants experienced a fall during the experiments. A single video recording was used to quantify the average speed, measured by the total distance walked over time for each lap, the number of

times the participant's made a foot placement error and made contact with a marker on the ground (i.e., contact errors), and the number of times a directional or planning error (i.e., trajectory errors) was made.

Imaging protocol

The data presented here was collected in the context of other studies with identical experimental procedure. Therefore, for six of seven young and two of seven middle-aged subjects, PET images were acquired on a Siemens High Resolution Research Tomograph (HRRT) PET scanner (CTI/Siemens, Knoxville, Tennessee). The spatial resolution is 2.3-3.4 mm at full-width-at-half-maximum (FWHM) (32). 3D sinograms were generated from the list-mode data acquired over 20 minutes, and reformatted into a series of eight 3D images of 5 minutes each to allow for normalization and correction of motion artefacts, random events, and scatter prior to summation of frames into one single 20-minute duration frame. The emission scan was followed by a 10-minute transmission scan for attenuation correction. For the remaining subjects, PET images were acquired on an ECAT EXACT HR^{+} scanner with a 20-minute emission scan (Siemens AG, Erlangen, Germany). The head was placed in the centre of the gantry and supported by a foam cushion and immobilized by a VELCRO strap for the duration of the scans.

T1-weighted images were acquired on a 3T Siemens TrioTrim Scanner (Siemens, Knoxville, TN) using a 3D magnetization prepared rapid gradient echo. T1 images were acquired as $1mm^3$ voxel sizes (echo time = 2.98ms; repetition time =23ms; flip angle= 9°). 240 parallel axial slices (thickness = 1mm) were obtained using an echo-planar imaging sequence (field of view = 240 X 256 mm^2). PET images were co-registered with T1-weighted imaged to specify regions of increased and decreased glucose metabolism.

Image Analysis

Statistical parametric mapping software SPM12 (Wellcome Department of Cognitive Neurology, London) implemented in MATLAB R2015a (MathWorks, Natick, MA, USA) was used for image processing and statistical analysis. The reconstructed PET images from each condition were linearly co-

registered with each subjects' T1-weighted image and spatially normalized to the ICBM 152 6th generation linear brain atlas (MNI, McGill University, Montreal, Canada) using a 12 parameter affine algorithm (33, 34). A Gaussian filter (FWHM= 12mm) was applied to all PET images in order to increase the signal-to-noise ratio. HRRT PET images were additionally smoothed with a Gaussian filter (FWHM= 6mm) prior to spatial normalization to compensate for the resolution differences between the two scanners. Finally, counts in each voxel were scaled to reach an average voxels count value of 50.

rCMRGluc during steering was directly compared with rCMRGluc during straight walking to determine task-related activations for both groups using whole-brain voxel-wise analysis in a flexible factorial design using factors: subject, group, and task. Main effects of task and group and their interaction was determined at $p<0.005$ and a cluster extent threshold of 30 voxels.

Statistical Analysis of gait performance

IBM SPSS (version 21.0, IBM, Armonk, NY, USA) was used for statistical comparison of gait performance. Non-parametric Mann Whitney U and Wilcoxon signed rank tests determined main effects of group (i.e., young and middle-aged) and task (straight and steering), respectively, since gait performance variables were non-parametric as determined by Shapiro-Wilk tests ($p<0.05$). For these analyses, medians and interquartile range are reported. Last, Pearson correlation coefficients for each subject's peak activation in significant clusters were determined for gait speed and the percent difference speed between tasks (i.e., difference speed = [straight walking speed-steering walking speed]/straight walking speed).

Results

rCMRGluc during Steering of Gait in Young and Middle-aged adults

Steering during gait increased rCMRGluc for both young and middle-aged adults in the superior parietal lobule (7A), superior frontal gyrus (BA 6), and cerebellum bilaterally, as well as in the right middle frontal gyrus (dorsolateral prefrontal cortex [BA 9]) (Figure 2; Table 1). There was decreased metabolic uptake during steering compared to straight walking for both young and middle-aged adults bilaterally in the inferior frontal [BA 44, 46]), occipital (middle, inferior [BA 18, 19]) gyri, and the precentral gyrus [BA 6]. Young adults also had deactivation of the left inferior parietal lobule (BA 40), and temporal (superior, inferior [BA 38, 20]) gyri, whereas middle-aged adults had deactivation of the middle cingulate cortex (BA 23, 24).

Group comparisons revealed that during steering, cerebral activity increased more in middle-aged adults, compared to young adults, at the level of the left precentral gyrus (BA 6) and right fusiform gyrus (BA 37) (Table 2a, Figure 3A) while activity increased less in middle-aged adults in the right dorsolateral prefrontal cortex (middle frontal gyrus [BA 9]), cuneus (BA 19), and the cerebellum with extension to the posterior mesencephalon (Table 2b, Figure 3B). Middle-aged adults also had less deactivation during steering of the inferior frontal gyrus bilaterally (BA 11), as well as the left postcentral gyrus (BA 4), fusiform gyrus (BA 20), precentral gyrus (BA 6), and middle frontal gyrus (BA 9) (Table 2d, Figure 3D) and more deactivation in the middle and anterior cingulate cortices (BA 31, 24), right inferior frontal gyrus (BA 11, 44), left cuneus, and the left putamen compared to young adults (Table 2c, Figure 3C).

Gait performance

Young and middle-aged adults had similar walking performance. During steering of gait, both groups walked slower ($p<0.05$) and made more trajectory errors (Steering, Middle-aged Adults: 6 ± 1, Young Adults: 2 ± 3; Straight walking, Middle-aged Adults: 0 ± 0, Young Adults: 0 ± 0, $p<0.05$) compared to straight walking. Middle-aged adults walked faster than young adults during straight walking (Middle-aged Adults: 1.34 ± 0.04, Young Adults: 1.08 ± 0.17 m/s, $p<0.01$), but not during steering of gait (Middle-aged Adults: 0.81 ± 0.14; Young Adults: 0.86 ± 0.08 m/s, $p=0.32$). Percent difference in speed

showed that middle-aged adults slowed down more for steering compared to young adults (Middle-aged Adults: -39 ± 1 %, Young Adults: -21 ± 1 %, $p<0.01$).

Discussion

We observed significant changes in brain metabolic activity associated with complex gait in middle-aged compared to young adults, who demonstrated similar changes in gait behavior. Most brain regions involved in steering of gait were generally preserved in middle-age, however, despite similar walking performance, there were important differences in activation distribution. More specifically, compared to young adults, middle-aged adults had (i) increased activation of the precentral and fusiform gyri, (ii) reduced activation of regions involved in cognitive control (middle frontal gyrus), and (iii) reduced deactivation of multisensory cortices (inferior frontal gyrus, postcentral gyrus, fusiform gyrus) when comparing gait steering to a control task of straight walking. Our results therefore suggest that changes in central sensorimotor processing related to complex walking are observed in middle-age and largely precede clinical changes in gait performance.

Frontoparietal network for complex locomotion preserved in middle-age

During steering of gait, both groups increased metabolic activity in frontoparietal regions that are particularly important for implementing visuomotor control of complex gait and integrating external information and internal movement-related goals, which is needed for accomplishing the complex walking task employed here (35, 36). In addition, the observed parietal and dorsolateral prefrontal

activations for steering in both groups indicates involvement of the cognitive control network known to be involved in goal-oriented behavior for complex locomotion (37, 38). The present findings are in line with evidence from imagined locomotion demonstrating that functional activation during mental imagery of forward simple gait is preserved in older adults (18). In addition, similar frontoparietal regions are activated during mental imagery of complex walking tasks (i.e., obstacle negotiation, backward walking), relative to imagery of simple forward walking, in older adults and individuals with Parkinson's disease (39-41). Our findings illustrate that executive control via a fronto-parietal network is required for over ground steering, a control mechanism that is largely preserved in middle-age.

Metabolic changes in middle-aged adults

Middle-aged adults demonstrate a larger increase in activity as compared to straight walking when executing a steering of gait task than what is found in young adults in the fusiform gyrus, and at the same time reduced deactivation of multisensory cortical regions (inferior frontal gyrus, postcentral gyrus, fusiform gyrus). These observations are in line with a recent investigation of age-effects on the locomotor network which shows an age-dependent increase in activity of multisensory cortical areas during imagined walking in older adults, a result that is thought to reflect impaired reciprocal inhibition of sensory interaction during locomotion in elderly individuals (18). Furthermore, our findings suggest that this process is already active in middle-age, observable under complex walking conditions.

Middle-aged adults also demonstrated reduced activation of occipital regions (i.e., cuneus) in addition to the middle frontal gyrus (i.e., dorsolateral prefrontal cortex) during steering of gait. These regions are part of the dorsal stream for visual processing, known to be critically involved in spatial navigation (42). Notably, occipital cortices are uniquely engaged during real locomotion (23). This is the first study to show increased activity in the dorsal pathway associated with complex locomotion. Visual stimuli are known to increase activity in visual cortices and decrease activity of cortices for other sensory modalities (i.e., vestibular, somatosensory, auditory) in young adults to a greater extent than in older

adults (19, 20). Thus, the decreased change in activity of occipital regions in middle-aged adults combined with increased multimodal associative cortices likely represents poor reciprocal inhibition of multisensory cortices and may be an early marker of age-related gait impairments (18).

Middle-aged adults in the present study did not have significant activation of cortical regions involved in executive functions. Instead, young adults showed larger increases in activation of the dorsolateral prefrontal cortex, precuneus, and superior occipital gyrus linked to steering than middle-aged adults. The dorsolateral prefrontal cortex together with the parietal cortex and caudate make up the cognitive control network that has been shown previously to be implicated in age-related gait impairment (16, 17, 43). Our results could either mean that, during steering of gait, these cognitive processing regions are not yet compensating for age-related cognitive and sensorimotor decline, or that middle-aged adults already require increased executive control during straight walking. On the other hand, it is possible that we were unable to detect slight changes in cognitive function here due to the small sample size and since previous reports indicate that there is a large inter-subject variability in cognitive functions in middle-aged individuals, especially underlying motor processing (15).

Middle-aged adults had significantly reduced change in activity of the posterior mesencephalon. This region is anatomically part of the mesencephalic locomotor region, composed of the pedunculopontine and cuneiform nuclei (44). This finding is different from those of Zwergal, Linn, Xiong, Brandt, Strupp and Jahn (18), who demonstrated no age-dependent activation of the mesencephalic locomotor region during imagined locomotion. However, this could be explained by modality differences, where mental imagery of simple gait was used as compared to the present study involving complex upright locomotion. Importantly, this region has previously been suggested to be involved in age-related gait disorders. In particular, individuals with progressive supranuclear palsy demonstrate hypoactivity of the mesencephalic locomotor region at rest and during imagined stance (25). Therefore, our results might illustrate early onset of age-related degradation of locomotor networks for complex locomotion involving the mesencephalic locomotor region.

During complex locomotion there was an increase in global cerebellar metabolism in both young and middle-aged adults. This finding is in line with previous studies of real and imagined simple and complex (i.e., obstacle negotiation tasks) gait and likely represents the cerebellum's known role in rhythmic modulation of locomotion (21, 23, 45, 46). The cerebellum plays a critical role in dynamic posture and trunk control, such as that required for continuous changes in the path of a walking subject (47, 48). A salient finding from the present study was that young adults activated both cerebellar hemispheres and the vermis, whereas middle-aged adults only activated the cerebellar hemispheres. Previously, it has been determined that the midline of the cerebellum is more involved in postural control, whereas the cerebellar hemispheres are related to leg positioning (45, 48). Due to the upright modality used here, these results could indicate that middle-aged adults allocate more resources for leg placement. This may be explained by several factors, such as impaired postural or dynamic stability, greater abdominal mass, or decreased body awareness. This is further supported by kinematic evidence for impaired trunk control in late-middle-aged and older adults (5). Moreover, the observed activation in the cerebellum during steering is likely due to continuous temporal and spatial modulation and dynamic postural control required for steering, aspects affected in healthy aging.

Limitations

The current study measured ^{18}F-FDG uptake over a period of 40 minutes: and thus results reflect the average metabolic activity throughout the entire task (49). This measure is insensitive to minor events such as the few simple turns during straight walking. In addition, group differences in scanner resolution was controlled for in preprocessing of images, though it cannot be ruled out that scanner type had an effect on the results. As shown in the Supplementary Figure, this effect was much smaller than the group effects observed. Another limitation is the differences in gait speed between groups. Although, both groups were instructed to walk at a "normal everyday walking pace", young adults self-selected speed was much slower than middle-aged adults during straight walking, whereas there was no difference between groups during steering. Indeed, this may confound our results, such that middle-aged adults may

already be engaging more cognitive resources to maintain a faster speed during their baseline gait task. Finally, these results should be considered carefully due to the small sample size, but warrant further investigations of cerebral adaptations for locomotor control in middle-age to better understand preclinical changes in neural function.

Conclusions

The unique paradigm used here allowed us for the first time to isolate steering of gait from straight walking during a real gait paradigm as opposed to mental imagery of gait, and demonstrate early changes in neural control of complex walking. To the best of our knowledge, this is the first study to evidence brain metabolic changes for complex locomotor control in middle-aged individuals. In particular, we show that middle-aged adults have impaired central sensorimotor processing linked to complex walking. This is likely due to age-related decline of peripheral inputs and decreased capacity of central structures to integrate peripheral information (i.e., normal or degraded) (50). Importantly, this age-related difference observed in the central motor control for locomotion seems to arise prior to the onset of observable changes in gait performance.

Funding

This work was supported by the Heart and Stroke Foundation of Canada, Canada Foundation for Innovation, and the Natural Sciences and Engineering Research Council of Canada.

Acknowledgements

The authors would like to thank the technicians at the PET and MRI units of the McConnell Brain Imaging Centre for their support in coordinating this project.

References

1. Hausdorff JM. Gait dynamics, fractals and falls: finding meaning in the stride-to-stride fluctuations of human walking. Hum Mov Sci. 2007;**26**:555-589.

2. Herman T, Mirelman A, Giladi N, Schweiger A, Hausdorff JM. Executive control deficits as a prodrome to falls in healthy older adults: a prospective study linking thinking, walking, and falling. J Gerontol A Biol Sci Med Sci. 2010;**65**:1086-1092.

3. Galna B, Peters A, Murphy AT, Morris ME. Obstacle crossing deficits in older adults: a systematic review. Gait Posture. 2009;**30**:270-275.

4. Courtine G, Schieppati M. Human walking along a curved path. II. Gait features and EMG patterns. Eur J Neurosci. 2003;**18**:191-205.

5. Lowry KA, Lokenvitz N, Smiley-Oyen AL. Age- and speed-related differences in harmonic ratios during walking. Gait Posture. 2012;**35**:272-276.

6. Jahn K, Deutschlander A, Stephan T, Kalla R, Hufner K, Wagner J*, et al.* Supraspinal locomotor control in quadrupeds and humans. Prog Brain Res. 2008;**171**:353-362.

7. DeLong MR, Wichmann T. Circuits and circuit disorders of the basal ganglia. Arch Neurol. 2007;**64**:20-24.

8. Armstrong DM, Drew T. Discharges of pyramidal tract and other motor cortical neurones during locomotion in the cat. J Physiol. 1984;**346**:471-495.

9. Liddell EG, Phillips CG. Striatal and pyramidal lesions in the cat. Brain. 1946;**69**:264-279.

10. Drew T, Prentice S, Schepens B. Cortical and brainstem control of locomotion. Prog Brain Res. 2004;**143**:251-261.

11. Heuninckx S, Wenderoth N, Swinnen SP. Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. J Neurosci. 2008;**28**:91-99.

12. Venkatraman VK, Aizenstein H, Guralnik J, Newman AB, Glynn NW, Taylor C*, et al.* Executive control function, brain activation and white matter hyperintensities in older adults. Neuroimage. 2010;**49**:3436-3442.

13. Salthouse TA. When does age-related cognitive decline begin? Neurobiol Aging. 2009;**30**:507-514.

14. Singh-Manoux A, Kivimaki M, Glymour MM, Elbaz A, Berr C, Ebmeier KP*, et al.* Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. BMJ. 2012;**344**:d7622.

15. Ferreira D, Machado A, Molina Y, Nieto A, Correia R, Westman E*, et al.* Cognitive Variability during Middle-Age: Possible Association with Neurodegeneration and Cognitive Reserve. Front Aging Neurosci. 2017;**9**:188.

16. Mirelman A, Maidan I, Bernad-Elazari H, Shustack S, Giladi N, Hausdorff JM. Effects of aging on prefrontal brain activation during challenging walking conditions. Brain Cogn. 2017;**115**:41-46.

17. Lewis SJ, Barker RA. A pathophysiological model of freezing of gait in Parkinson's disease. Parkinsonism Relat Disord. 2009;**15**:333-338.

18. Zwergal A, Linn J, Xiong G, Brandt T, Strupp M, Jahn K. Aging of human supraspinal locomotor and postural control in fMRI. Neurobiol Aging. 2012;**33**:1073-1084.

19. Peiffer AM, Hugenschmidt CE, Maldjian JA, Casanova R, Srikanth R, Hayasaka S*, et al.* Aging and the interaction of sensory cortical function and structure. Hum Brain Mapp. 2009;**30**:228-240.

20. Brandt T, Bartenstein P, Janek A, Dieterich M. Reciprocal inhibitory visual-vestibular interaction. Visual motion stimulation deactivates the parieto-insular vestibular cortex. Brain. 1998;**121 (Pt 9)**:1749-1758.

21. Jahn K, Deutschlander A, Stephan T, Kalla R, Wiesmann M, Strupp M*, et al.* Imaging human supraspinal locomotor centers in brainstem and cerebellum. Neuroimage. 2008;**39**:786-792.

22. Jahn K, Deutschlander A, Stephan T, Strupp M, Wiesmann M, Brandt T. Brain activation patterns during imagined stance and locomotion in functional magnetic resonance imaging. Neuroimage. 2004;**22**:1722-1731.

23. la Fougere C, Zwergal A, Rominger A, Forster S, Fesl G, Dieterich M*, et al.* Real versus imagined locomotion: a [18F]-FDG PET-fMRI comparison. Neuroimage. 2010;**50**:1589-1598.

24. Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? Age Ageing. 2006;**35 Suppl 2**:ii7-ii11.

25. Zwergal A, la Fougere C, Lorenzl S, Rominger A, Xiong G, Deutschenbaur L*, et al.* Postural imbalance and falls in PSP correlate with functional pathology of the thalamus. Neurology. 2011;**77**:101-109.

26. Zwergal A, la Fougere C, Lorenzl S, Rominger A, Xiong G, Deutschenbaur L*, et al.* Functional disturbance of the locomotor network in progressive supranuclear palsy. Neurology. 2013;**80**:634-641.

27. Zwergal A, Schoberl F, Xiong G, Pradhan C, Covic A, Werner P*, et al.* Anisotropy of Human Horizontal and Vertical Navigation in Real Space: Behavioral and PET Correlates. Cereb Cortex. 2015.

28. Tard C, Delval A, Devos D, Lopes R, Lenfant P, Dujardin K*, et al.* Brain metabolic abnormalities during gait with freezing in Parkinson's disease. Neuroscience. 2015;**307**:281-301.

29. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971;**9**:97-113.

30. Varrone A, Asenbaum S, Vander Borght T, Booij J, Nobili F, Nagren K*, et al.* EANM procedure guidelines for PET brain imaging using [18F]FDG, version 2. Eur J Nucl Med Mol Imaging. 2009;**36**:2103-2110.

31. Paquette C, Franzen E, Jones GM, Horak FB. Walking in circles: navigation deficits from Parkinson's disease but not from cerebellar ataxia. Neuroscience. 2011;**190**:177-183.

32. Funck T, Paquette C, Evans A, Thiel A. Surface-based partial-volume correction for high-resolution PET. Neuroimage. 2014;**102 Pt 2**:674-687.

33. Friston KJ, Ashburner J, Frith CD, Poline JB, Heather JD, Frackowiak RSJ. Spatial registration and normalization of images. Human Brain Mapping. 1995;**3**:165-189.

34. Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K*, et al.* A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). Philos Trans R Soc Lond B Biol Sci. 2001;**356**:1293-1322.

35. Mutha PK, Sainburg RL, Haaland KY. Left parietal regions are critical for adaptive visuomotor control. J Neurosci. 2011;**31**:6972-6981.

36. Battaglia-Mayer A, Caminiti R, Lacquaniti F, Zago M. Multiple levels of representation of reaching in the parieto-frontal network. Cereb Cortex. 2003;**13**:1009-1022.

37. Cole MW, Schneider W. The cognitive control network: Integrated cortical regions with dissociable functions. Neuroimage. 2007;**37**:343-360.

38. Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. J Neurophysiol. 2008;**100**:3328-3342.

39. Maidan I, Rosenberg-Katz K, Jacob Y, Giladi N, Deutsch JE, Hausdorff JM*, et al.* Altered brain activation in complex walking conditions in patients with Parkinson's disease. Parkinsonism Relat Disord. 2016;**25**:91-96.

40. Wai YY, Wang JJ, Weng YH, Lin WY, Ma HK, Ng SH*, et al.* Cortical involvement in a gait-related imagery task: comparison between Parkinson's disease and normal aging. Parkinsonism Relat Disord. 2012;**18**:537-542.

41. Maidan I, Nieuwhof F, Bernad-Elazari H, Reelick MF, Bloem BR, Giladi N*, et al.* The Role of the Frontal Lobe in Complex Walking Among Patients With Parkinson's Disease and Healthy Older Adults: An fNIRS Study. Neurorehabil Neural Repair. 2016;**30**:963-971.

42. Kravitz DJ, Saleem KS, Baker CI, Mishkin M. A new neural framework for visuospatial processing. Nat Rev Neurosci. 2011;**12**:217-230.

43. Shine JM, Moustafa AA, Matar E, Frank MJ, Lewis SJ. The role of frontostriatal impairment in freezing of gait in Parkinson's disease. Front Syst Neurosci. 2013;**7**:61.

44. Jordan LM. Initiation of locomotion in mammals. Ann N Y Acad Sci. 1998;**860**:83-93.

45. Mori S, Matsui T, Kuze B, Asanome M, Nakajima K, Matsuyama K. Stimulation of a restricted region in the midline cerebellar white matter evokes coordinated quadrupedal locomotion in the decerebrate cat. J Neurophysiol. 1999;**82**:290-300.

46. Armstrong DM. The supraspinal control of mammalian locomotion. J Physiol. 1988;**405**:1-37.

47. Asanome M, Matsuyama K, Mori S. Augmentation of postural muscle tone induced by the stimulation of the descending fibers in the midline area of the cerebellar white matter in the acute decerebrate cat. Neurosci Res. 1998;**30**:257-269.

48. Ilg W, Giese MA, Gizewski ER, Schoch B, Timmann D. The influence of focal cerebellar lesions on the control and adaptation of gait. Brain. 2008;**131**:2913-2927.

49. Sarikaya I. PET studies in epilepsy. Am J Nucl Med Mol Imaging. 2015;**5**:416-430.

50. Goble DJ, Coxon JP, Wenderoth N, Van Impe A, Swinnen SP. Proprioceptive sensibility in the elderly: degeneration, functional consequences and plastic-adaptive processes. Neurosci Biobehav Rev. 2009;**33**:271-278.

Figure Legends

Figure 1. Schematic of locomotor tasks.

A subset of the task showing the (A) straight walking task where subjects were instructed to remain in the middle of the walking lane and make 180 degree turns into the next lane and (B) steering of gait trajectory where subjects were instructed to steer around yellow colored cones, indicated by light grey in the figure. The remaining cones were orange, indicated by dark grey. The entire experimental setup consisted of 150 cones arranged in 5 rows of 30 cones spanning the length of the 28 m long and 1.2 m wide walking lanes.

Figure 2. Increased rCMRGluc during steering of gait (steering>straight walking)

Results from the whole-brain analysis. (A) Middle-aged adults had prominent activations of the superior parietal lobule, superior frontal gyrus, the right dorsolateral prefrontal cortex, and cerebellar lobules. (B): Young adults had activations of the superior parietal lobule, superior frontal gyrus, the right dorsolateral prefrontal cortex cerebellar lobules, as well as the posterior mesencephalon. $P<0.005$ (uncorr.), cluster extent threshold=30, color bars represent t-values.

Figure 3. Differences between groups in steering-related rCMRGluc

Results from the whole-brain analysis showing significant interaction effects. (A) Increased activation (steering>straight) in middle-aged adults compared to young adults during steering in the precentral and fusiform gyri. (B) Increased activation in young adults was mainly in the middle frontal gyrus, cuneus, and cerebellum with extension to the posterior mesencephalon. (C) Increased deactivation (steering<straight) in middle-aged adults was observed mainly in the anterior and middle cingulate cortices and cuneus. (D) Increased deactivation in young adults was observed in multisensory cortices

(inferior frontal gyrus, postcentral gyrus, fusiform gyrus) P<0.005 (uncorr.), cluster extent threshold=30, color bars represent t-values.

Table 1: Task effects of rCGM during simple and complex locomotion

a) Middle-aged adults

Increased metabolism (steering>straight)								
Cerebral hemispheres	**BA**	**Cluster**	***Z***	***T***	***P***	**x**	**y**	**z**
R/L superior parietal lobule	7	3096	4.76 4.20 4.25	8.54 6.55 6.71	**<0.001** **<0.001** **<0.001**	-22 -4 18	-62 -68 -58	66 62 68
R/L superior frontal gyrus	6	292 337	4.00 3.62 3.13	5.98 5.03 4.01	<0.001 <0.001 0.001	30 -20 -32	0 -6 -6	62 66 58
R posterior-medial frontal	6	105	3.40	4.54	<0.001	12	4	72
L posterior cingulate cortex	31	215	3.20 2.89 2.63	4.13 3.57 3.13	0.001 0.002 0.004	-22 -24 -28	-66 -58 -54	16 2 18
R anterior Cingulate Cortex	24	34	2.83	3.46	0.002	-2	32	-6
R middle frontal gyrus	9	35	2.78	3.37	0.003	38	40	32
Cerebellum & Brainstem								
R cerebellum	VI	644	3.99 3.77	5.96 5.38	<0.001 <0.001	30 38	-48 -58	-30 -24
R cerebellum	VI	80	3.76	5.36	<0.001	10	-72	-20
L cerebellum	Crus I	132	2.97	3.72	0.001	-38	-60	-30
Decreased metabolism (steering<straight)								
Cerebral hemispheres	**BA**	**Cluster**	***Z***	***T***	***P***	**x**	**y**	**z**
R/L inferior frontal gyrus	46	731 499	4.01 2.66 3.29 3.19 2.94	6.01 3.19 4.31 4.11 3.66	<0.001 0.004 0.001 0.001 0.002	-56 -54 40 52 52	34 38 4 4 4	10 -14 24 -12 12
R/L superior medial frontal	8	1130	3.97 3.92	5.92 5.77	<0.001 <0.001	10 4	30 22	40 50

gyrus		179	3.42	4.59	<0.001	12	48	36
			3.36	4.47	<0.001	-4	54	48
L superior temporal gyrus, inferior frontal gyrus	22, 44	380	3.87	5.65	<0.001	-66	-18	6
			3.03	3.82	0.001	-64	-2	10
R/L middle orbital gyrus	11	812	3.84	5.55	<0.001	0	56	-2
			3.52	4.80	<0.001	22	44	6
			3.31	4.35	<0.001	14	46	-10
L middle cingulate cortex	23, 24	653	3.77	5.38	<0.001	-8 -	-44	34
			3.36	4.46	<0.001	20	-22	40
			3.24	4.21	0.001	-10	-12	34
R postcentral gyrus	2	82	3.61	5.01	<0.001	42	-22	28
L middle frontal gyrus	9	75	3.54	4.85	<0.001	-54	22	36
L cuneus	18,19	421	3.53	4.81	<0.001	-10	-92	16
			3.14	4.01	<0.001	-16	-98	8
R/L precentral gyrus	6	427	3.46	4.55	<0.001	36	-22	60
		431	3.40	4.67	<0.001	-30	20	74
RL lingual gyrus	18	41	2.88	3.55	0.002	-8	-80	-10
		32	2.82	3.45	0.002	24	-80	-10
L superior frontal gyrus	8	328	3.19	4.11	0.001	-20	32	46
			3.10	3.95	0.001	-32	20	62
L putamen		39	2.82	3.46	0.002	-20	18	-2
L insula	13	48	2.78	3.39	0.003	-32	10	24
R fusiform gyus, lingual gyrus	18, 19	97	2.90	3.59	0.002	32	-82	-22
			2.89	3.57	0.002	24	-82	-8
Cerebellum & Brainstem								
No clusters								

b) Young adults

Increased metabolism (steering>straight)								
Cerebral hemispheres	**BA**	**Cluster**	***Z***	***T***	***P***	**x**	**y**	**z**

R/L superior parietal lobule	7	3044	5.00 4.61 4.50	9.57 7.96 7.54	**<0.001** **<0.001** **<0.001**	-24 8 20	-62 -56 -60	66 68 68
R middle frontal gyrus	9	324	3.12	3.99	0.001	42	30	30
R/L superior frontal gyrus	6	63 167	2.94 3.44	3.65 4.63	0.002 <0.001	14 -20	-2 -4	78 72
R middle temporal gyrus	39	535	3.06 3.05	3.87 3.85	0.001 0.001	42 32	-62 -54	10 20
R Insula	13	48	3.11	3.96	0.001	40	-28	24
L Cuneus	18, 19	121	3.03 2.96	3.81 3.69	0.001 0.002	-10 -6	-90 -78	26 18
Cerebellum & Brainstem								
R cerebellum	IV-V, VI	845	3.58 3.03	4.94 3.82	<0.001 0.001	4 12	-40 -46	-10 -6
R cerebellum	VI	1639	3.54 3.19	4.84 4.11	<0.001 0.001	34 26	-42 -44	-34 -62
L cerebellum	VII, VIII	1572	3.34 3.28	4.41 4.29	<0.001 0.001	-32 -34	-36 -40	-40 -54
cerebellar vermis		90	2.79	3.40	0.003	0	-68	-42
Decreased metabolism (steering<straight)								
Cerebral hemispheres	**BA**	**Cluster**	***Z***	***T***	***P***	**x**	**y**	**z**
L middle frontal gyrus	4, 6	2364	4.24 4.22 3.87	6.69 6.61 5.63	**<0.001** **<0.001** **<0.001**	-40 -38 -34	6 8 -30	52 60 66
R superior medial gyrus	13, 41	998	4.10 3.42 3.08	6.26 4.59 3.91	<0.001 <0.001 0.001	10 8 16	42 44 60	-18 0 -2
L middle, inferior occipital gyri	17, 18 19	1848	3.71 3.62 3.28	5.23 5.02 4.30	<0.001 <0.001 0.001	-44 -34 -46	-86 -80 -76	0 -22 -12

L precentral gyrus, insula	6, 13	526	3.70 3.33 2.74	5.23 4.41 3.32	<0.001 <0.001 0.003	-40 -42 -54	-26 -14 -4	12 14 10
L inferior parietal lobule	40	465	3.56	4.89	<0.001	-48	-66	46
L inferior frontal gyrus	44, 45	728	3.36 3.02 2.97	4.47 3.79 3.72	<0.001 0.001 0.001	-56 -48 -56	32 30 36	6 22 -10
R inferior occipital gyrus, lingual gyrus	18, 19	1261	3.32 3.28 3.17	4.38 4.31 4.08	<0.001 0.001 0.001	26 34 36	-86 -92 -82	-8 - 6 - 20
L inferior temporal gyrus	20	71	3.07	3.89	0.001	-64	-48	-18
L fusiform gyrus	20	69	2.87	3.54	0.002	-56	-22	-32
L superior temporal lobe	38	32	2.76	3.34	0.003	-48	14	-34
Cerebellum & Brainstem								
No clusters								

Significance level p<0.005, uncorrected; cluster extent threshold 30; R: right, L: left, Cluster: cluster size in voxels, Z: Z-value, *T*: T-value, *P*: p-value; x, y, z: coordinates in MNI space. Indicated in bold type are clusters that survived FDR correction.

Table 2: Group effects of rCGM during simple and complex locomotion

a) Middle-aged Adults > Young for activations (steering>straight walking)

Cerebral hemispheres	**BA**	**Cluster**	***Z***	***T***	***P***	**x**	**y**	**z**
R fusiform gyrus	37	102	3.77	5.38	<0.001	38	-58	-24
L precentral gyrus	6	41	3.13	4.01	0.001	-32	-6	58
Cerebellum & Brainstem								
No clusters								

b) Young > Middle-aged Adults for activations (steering>straight walking)

Cerebral hemispheres	BA	Cluster	*Z*	*T*	*P*	x	y	z
R middle frontal gyrus	9	48	3.11	3.96	<0.001	50	30	32
L cuneus	19	67	3.03	3.81	<0.001	-10	-90	26
Cerebellum & Brainstem								
R cerebellum (III)		33	2.87	3.53	0.002	8	-38	-20

c) Middle-aged > Young Adults for deactivations (steering<straight walking)

Cerebral hemispheres	BA	Cluster	*Z*	*T*	*P*	x	y	z
R inferior frontal gyrus	11, 44	56	3.29	4.31	0.001	40	4	24
L middle cingulate cortex	31	47	3.61	5.01	<0.001	-8	-44	34
R anterior cingulate cortex	24	72	3.15	4.05	0.001	0	0	30
L cuneus	19	176	3.53	4.82	<0.001	-10	-92	16
R Putamen		25	2.82	3.46	0.002	-20	18	-2
Cerebellum & Brainstem								
No clusters								

d) Young > Middle-aged Adults for deactivations (steering<straight walking)

Cerebral hemispheres	BA	Cluster	*Z*	*T*	*P*	x	y	z
R inferior frontal gyrus	11	206	4.10	6.26	<0.001	10	42	-18
L middle frontal gyrus	9	255	4.24	6.69	<0.001	-40	6	52
L fusiform gyrus	20	36	2.87	3.54	0.002	-56	-22	-32
L postcentral gyrus	4	90	3.80	5.46	<0.001	-34	-30	64
			3.64	5.08	<0.001	-46	-26	62
L precentral gyrus	6	64	3.38	4.51	<0.001	-50	-2	42
Cerebellum & Brainstem								
No clusters								

Significance level p<0.005, uncorrected; cluster extent threshold 30; R: right, L: left, Cluster: cluster size in voxels, Z: Z-value, *T*: T-value, *P*: p-value; x, y, z: coordinates in MNI space

Figure 1

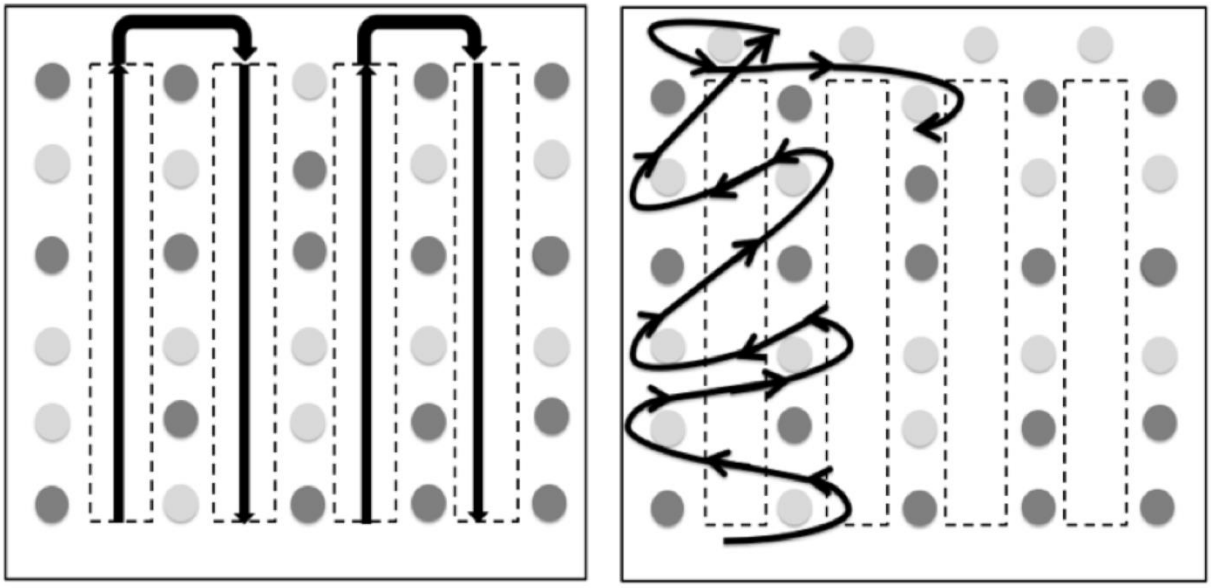

Figure 2

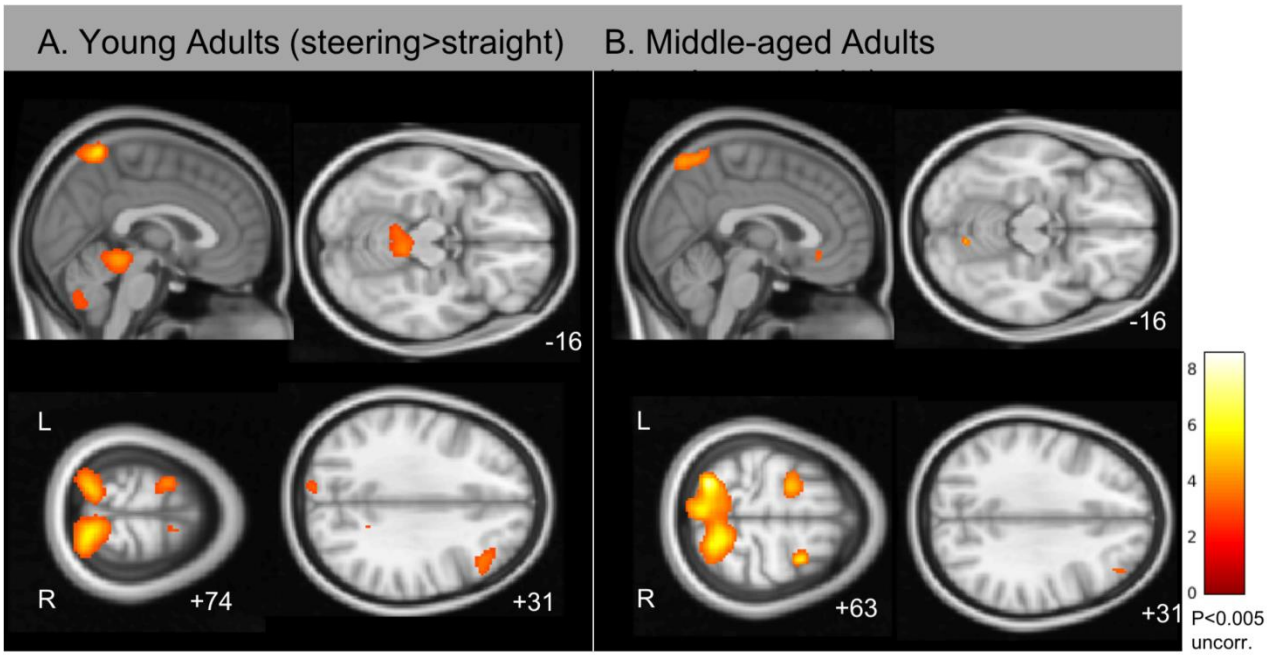

Figure 3