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Behavioral and Neural Correlates of Imagined Walking and Walking-While-Talking in the Elderly

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Abstract: Cognition is important for locomotion and gait decline increases the risk for morbidity, mortality, cognitive decline, and dementia. Yet, the neural correlates of gait are not well established, because most neuroimaging methods cannot image the brain during locomotion. Imagined gait protocols overcome this limitation. This study examined the behavioral and neural correlates of a new imagined gait protocol that involved imagined walking (iW), imagined talking (iT), and imagined walking-while-talking (iWWT). In Experiment 1, 82 cognitively-healthy older adults ($M = 80.45$) walked (W), iW, walked while talking (WWT) and iWWT. Real and imagined walking task times were strongly correlated, particularly real and imagined dual-task times (WWT and iWWT). In Experiment 2, 33 cognitively-healthy older adults ($M = 73.03$) iW, iT, and iWWT during functional magnetic resonance imaging. A multivariate Ordinal Trend (OrT) Covariance analysis identified a pattern of brain regions that: (1) varied as a function of imagery task difficulty (iW, iT and iWWT), (2) involved cerebellar, precuneus, supplementary motor and other prefrontal regions, and (3) were associated with kinesthetic imagery ratings and behavioral performance during actual WWT. This is the first study to compare the behavioral and neural correlates of imagined gait in single and dual-task situations, an issue that is particularly relevant to elderly populations. These initial findings encourage further research and development of this imagined gait protocol as a tool for improving gait and cognition among the elderly. *Hum Brain Mapp 35:4090–4104, 2014.* © 2014 Wiley Periodicals, Inc.

Key words: gait; imagery; dual-task; fMRI and aging

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INTRODUCTION

Motor imagery involves asking individuals to envision themselves executing motor actions, without actual execution [Jeannerod, 1994]. Motor imagery is an effective rehabilitative tool that improves motor actions in individuals with Parkinson's disease [Heremans et al., 2011; Tamir et al., 2007] and post stroke [Dunsky et al., 2008; Kim et al., 2011; Verma et al., 2011]—presumably because it activates the same or similar neural systems as the actual execution of motor actions [Anderson and Lenz, 2011; Jeannerod, 2001]. This study examined the behavioral and neural correlates of imagined gait in cognitively-healthy older adults, with the ultimate goal of developing rehabilitative tools to improve gait and cognition in aging.

Gait decline is common in dementia, but also occurs in cognitively-healthy older adults. It is consistently observed in individuals with mild cognitive impairment (MCI) [Petersen, 2004; Petersen et al., 1999, 2009], Alzheimer's disease, and other forms of dementia [Verghese et al., 2002b, 2008, 2007b]. In cognitively-healthy older adults, gait decline is associated with an increased risk of future cognitive decline and dementia [Marquis et al., 2002; Verghese et al., 2007b; Waite et al., 2005; Wang et al., 2006]. It is also associated with an increased risk of morbidity, hospitalization, and mortality [Newman et al., 2006; Verghese et al., 2007b].

At this time, however, the neural correlates of gait are largely unexplored in humans. This is because noninvasive neuroimaging techniques such as functional magnetic resonance imaging (fMRI) cannot image the brain during locomotion. One solution to this problem is to examine the neural correlates of motor imagery or imagined gait. Another solution is to use a more invasive radioactive imaging technique such as [^{18}F]-Flouro-Deoxy-Glucose Positron Emission Tomography (FDG-PET) [la Fougere et al., 2010]. More specifically, [^{18}F] FDG-PET can be used to study the neural correlates of actual gait by tracking glucose utilization shortly following walking.

Recent motor imagery studies using fMRI suggest that imagined gait engages cerebellar, basal ganglia, supplementary motor and other prefrontal cortex regions to a greater extent than imagined lying or standing [Cremers et al., 2012; Jahn et al., 2004, 2008; van der Meulen et al., in press]—and results are fairly similar in cognitively-healthy older adults compared with younger adults [Zwergal et al., 2012]. An [^{18}F] FDG-PET and fMRI comparison of actual walking and imagined walking (iW) has confirmed these regional brain activity findings, as well as extended them by showing that walking engages the primary motor cortex to a greater extent than iW, while iW engages supplementary motor regions to a greater extent than actual walking [la Fougere et al., 2010]. The neural correlates of imagined gait in more complex dual-task situations such as imagined walking-while-talking are currently unknown.

Age-related gait decline is particularly evident in dual-tasks where individuals are asked to walk while performing a secondary cognitive task such as memorizing a list of words, reciting alternate letters of the alphabet, or talking on a cell phone [Beurskens and Bock, 2012; Buracchio et al., 2010; Holtzer et al., 2006, 2011, 2012b; Li et al., 2001; Lindenberger et al., 2000; Neider et al., 2011; Verghese et al., 2002a]. The typical finding in these situations is that dual-task costs [Kahneman, 1973; Pashler, 1984]—the decrement in performance observed in dual-tasks relative to single tasks—are greater among older adults than younger adults. A similar pattern of age-related differences are observed in dual-tasks that do not involve gait [for reviews see Hartley, 1992; McDowd and Shaw, 2000; Verhaeghen et al., 2003]. Walking while reciting alternate letters of the alphabet (WWT), developed by our group [Verghese et al., 2002a], was the dual-task that was adapted to examine the behavioral and neural correlates of imagined gait in this study. This dual-task was chosen primarily because performance on this task reliably predicts falls, frailty, disability, and mortality in cognitively-healthy older adults [Verghese et al., 2002a, 2012].

Dual-task performance is typically attributed to executive functions that are largely subserved by the prefrontal cortex [Stelzel et al., 2009; Szameitat et al., 2002], and particularly affected by aging [Davidson et al., 2006; Moscovitch, 1995; Shimamura et al., 1990; West, 1996]. Executive functions are a set of attention-demanding processes that monitor and coordinate complex behaviors that involve planning, reasoning, or the selection and inhibition of appropriate responses [Norman and Shallice, 1980]. Dual-task performance is considered a specific component of executive functions that involves allocating attention to competing task demands [Baddeley, 1996, 2001; Holtzer et al., 2004, 2005]. Age-related decline in executive functions, including dual-task performance, are typically attributed to reduced functional efficiency of prefrontal cortex regions, and signified by increased or decreased prefrontal cortex activation as a function of increased task difficulty among the elderly; e.g. when contrasting a single task to a dual-task [Cabeza et al., 1997; Erickson et al., 2007; Gazes et al., 2012; Grady et al., 1999; Reuter-Lorenz et al., 2000; Stern et al., 2012].

Age-related gait decline is also associated with a decline in executive functions. For example, poor gait performance is consistently associated with poor performance on conventional neuropsychological measures of executive functions [Atkinson et al., 2007; Holtzer et al., 2006, 2012a; Watson et al., 2010]. Training executive functions with a computerized remediation-program also improves actual gait in cognitively-healthy older adults on the Walking (W) and WWT task adapted for the current study [Verghese et al., 2010]. Thus, this WWT task was also adapted for this study because it demands a considerable amount of executive functions, and is therefore particularly challenging to older adults.

In Experiment 1, we examined the relationship between real and imagined W and WWT times. Our main prediction was that real and imagined W and WWT times would be correlated [Bakker et al., 2007; Beauchet et al., 2010].

In Experiment 2, we examined the neural correlates of iW, iT, and iWWT during fMRI scanning. We were particularly interested in identifying neural activation that change as a function of imagery task difficulty: iW, iT and iWWT. Although we expected neural activity in prefrontal regions to increase as a function of task difficulty, we used a whole-brain, data-driven, multivariate Ordinal Trend Covariance Analysis (OrT-CVA) to address this issue. This is because we were interested in determining how the use of the entire locomotion system (e.g. motor, basal ganglia, cerebellar, supplementary motor, and other prefrontal regions) change as a function of increasing task difficulty. This is also because changes in neural activation as a function of task difficulty are often masked by between-subject variability, an issue that is particularly important to consider in aging [Cabeza et al., 2002; Colcombe et al., 2005]. In fact, OrT-CVA was specifically developed to be more sensitive to task-related changes, and has been successfully used to identify regions of neural activation that change as a function of task difficulty previously [Habeck et al., 2005].

EXPERIMENT 1

Methods

Participants

A convenience sample of 82 cognitively-healthy (Short Blessed < 4 [Katzman et al., 1983; Morris et al., 1989]), non-depressed (Geriatric Depression Scale; GDS < 6 [Sheikh and Yesavage, 1986; Yesavage, 1988; Yesavage et al., 1982]) older adults (M Age = 80.45) enrolled in the Einstein Aging Study (EAS), which aims to identify risk factors for dementia, were recruited for this experiment. Demographic and screening information about our study-specific sample is provided in Table I. Additional details of the EAS study design has been reported elsewhere [Verghese et al., 2004]. In brief, older adults (>70 years) residing in Bronx County were first contacted via mail and then over the phone. Participants that provided verbal consent over the phone were then invited for in-person evaluations. Exclusion criteria included severe auditory or visual loss, bedbound due to illness, institutionalization, and presence of depression or dementia. Written consent was obtained and approved by the Committee on Clinical Investigations of the Albert Einstein College of Medicine in Bronx, NY.

Procedure

Participants were timed with a stopwatch while they walked a 14 feet course at their normal pace (W) and while they imagined walking (iW) the same 14 feet course. Participants were also timed while they walked this course and recited alternate letters of the alphabet out loud (WWT), and while they imagined walking this course while reciting alternate letters of the alphabet out loud (iWWT). Participants were always asked to complete the actual walking task before the imagined walking task (i.e. W then iW, WWT then iWWT). In the WWT and iWWT conditions, they were also instructed to pay equal attention to both tasks. Following iWWT, they were asked to describe their strategy for performing the dual-task and whether they managed to pay equal attention to both tasks [Verghese et al., 2007a]. All but three participants ($n = 79$) completed another normal pace walk (W-2) and Walking-While-Talking (WWT-2) trial following the iW and iWWT trial, respectively. A subset of our sample ($n = 43$) also completed the Vividness of Visual Imagery Questionnaire (VVIQ) [Marks, 1973, 1995] before the walking tasks. The VVIQ involves execution and imagery of five simple motor movements (e.g. forward shoulder flexion and foot tapping) followed by the evaluation of the quality of the visual and kinesthetic image for each movement on a scale from 1 (no image; no sensation) to 5 (image as clear as seeing; as intense as executing the action). The VVIQ has a maximum total score of 25 and a maximum mean score of 5 for visual imagery and kinesthetic imagery, respectively.

TABLE I. Mean and standard deviation (in parentheses) of demographic, screening, and survey information in experiment 1 and experiment 2

	Experiment 1	Experiment 2
Age	80.45(6.28)	73.03 (5.91)
% Female	56	45
Short-blessed	1.24 (1.17)	—
MIS	—	7.67(0.74)
GDS	1.36 (1.45)	4.00 (3.37)
Visual imagery VVIQ	3.87 (1.07)	3.34 (1.28)
Kinesthetic imagery VVIQ	3.10 (1.23)	2.53 (1.21)
Visual imagery training	—	3.29(0.86)[a]
Kinesthetic imagery training	—	2.58(0.83)[a]
Visual imagery MRI	—	2.73(1.23)
Kinesthetic imagery MRI	—	2.24 (1.09)

[a] Visual and kinesthetic imagery ratings did not differ during the first block of imagery training compared with the second block of imagery training ($P > 0.05$) and were therefore collapsed across blocks here and in the text.

RESULTS

The mean of the visual imagery ratings on the VVIQ was 3.87 (clear image) and the mean kinesthetic imagery ratings was 3.10 (moderately intense sensation; see Table I). As predicted, however, both WWT and iWWT times (M = 8.86 sec, SD = 4.89 sec, M = 12.26 sec, SD = 7.43 sec) were slower than W and iW times (M = 6.01 sec, SD = 1.66, M = 7.03 sec, SD = 3.07 sec), $t_{(81)} = 7.50$, $P < 0.001$ and $t_{(81)} = 6.14$, $P < 0.001$, respectively). A similar pattern of results was observed during the second walking (W-2; M = 5.80 sec, SD = 1.67 sec) and Walking-While-Talking (WWT-2; M = 9.16 sec, SD = 5.04 sec) trials, $t_{(78)} = 7.03$, $P < 0.001$. In

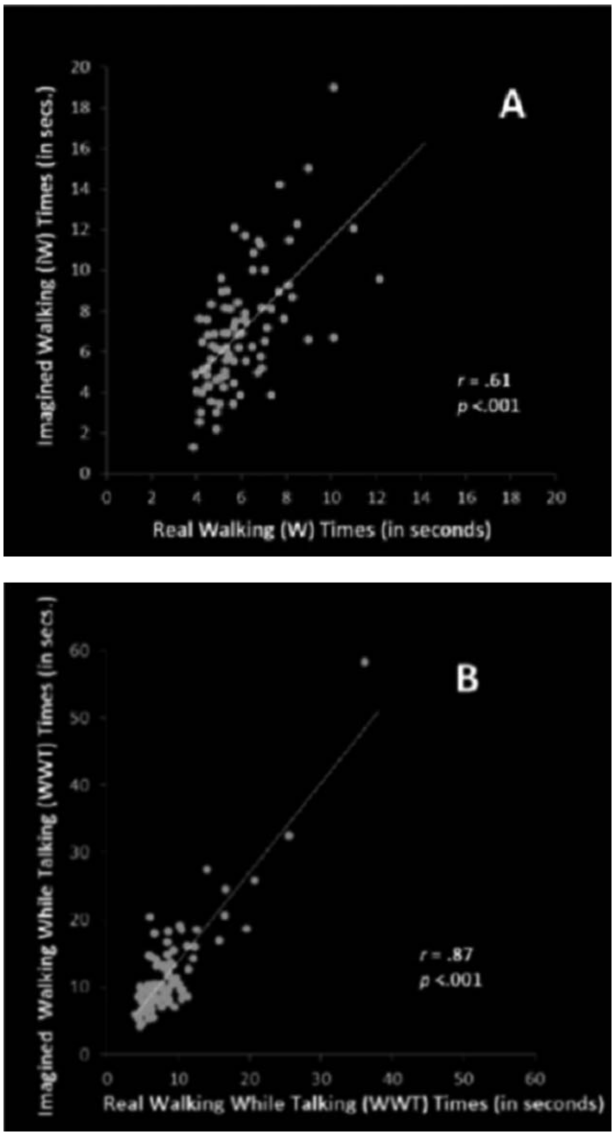

Figure 1.

The temporal correspondence between real and imagined walking tasks in Experiment 1. **A**. The correlation between real and imagined walking times. **B**. The correlation between real and imagined Walking-While-Talking times.

general, dual-task costs were greater during the imagined version of the task (iWWT-iW = 5.23 sec) compared with the real version of the tasks (WWT-W: 2.85 sec, WWT-2-W = 3.18 sec), $t_{(81)} = 5.45$, $P < 0.001$ and $t_{(79)} = 4.64$, $P < 0.001$, respectively. More importantly, W and iW times were highly correlated, $r = 0.61$, $P < 0.001$ (see Fig. 1A), and an even stronger correlation was observed between WWT and iWWT ($r = 0.87$, $P < 0.001$; see Fig. 1B; $z = 2.56$, $P < 0.05$). Similar correlations between real and imagined walking were observed during the second trial (W-2 and iW: $r = 0.75$, $P < 0.001$; WWT-2 and iWWT: $r = 0.87$, $P < 0.001$).

Of the 82 older adults in our study sample, 36 (43.9%) reported that during iWWT they paid equal attention to both tasks, 30 (36.6%) reported that they emphasized the letters, 3 (3.7%) reported that they emphasized walking, and 13 (15.9%) reported that they did not have an explicit strategy. The correlation between WWT and iWWT times were stronger among those that paid equal attention to both tasks (WWT and iWWT; $r = 0.90$, $P < 0.001$ and WWT-2 and iWWT; $r = 0.92$, $P < 0.001$) than those who emphasized reciting alternate letters of the alphabet (WWT and iWWT; $r = 0.68$, $P < 0.001$ and WWT-2 and iWWT; $r = 0.68$, $P < 0.001$), $z = 2.50$, $P < 0.05$ and $z = 2.91$, $P < 0.01$, respectively.

Finally, we divided our study sample according to whether their actual dual task performance (WWT-W time) were poor (the lowest tertile, ~33%) or strong (upper tertiles, ~66%)—as suggested by Bridenbaugh et al. [2013]. The correlation between W and iW was stronger among individuals that had poor dual task performance ($r = 0.79$, $P < 0.001$), than those who had strong dual-task performance ($r = 0.40$, $P < 0.05$), $z = 2.51$, $P < 0.05$). Similar patterns of results were observed during the second trial (lowest tertile: W-2 and iW: $r = 0.84$, $P < 0.001$; upper tertiles: W-2 and iW: $r = 0.53$, $P < 0.001$; $z = 2.51$, $P < 0.05$), and between WWT and iWWT during the first trial (lowest tertile: WWT-2 and iWWT: $r = 0.92$, $P < 0.001$; upper tertiles: WWT-2 and iWWT: $r = 0.57$, $P < 0.001$; $z = 3.90$, $P < 0.001$) and the second trial (lowest tertile: WWT-2 and iWWT: $r = 0.91$, $P < 0.001$; upper tertiles: WWT-2 and iWWT: $r = .64$, $P < 0.001$; $z = 3.11$, $P < 0.001$).[1]

EXPERIMENT 2

Methods

Participants

A convenience sample of 33 cognitively-healthy (Memory Impairment Screen (MIS) > 5 [Buschke et al., 1999; Lipton et al., 2003], nondepressed (*M* 15-item GDS = 4.00), and right-handed older adults (*M* age = 73.03) enrolled in the Central Control of Mobility in Aging (CCMA) study, which aims to identify cognitive and brain predictors of mobility were recruited for this experiment. Demographic and screening information about this sample is provided in Table I. Additional details of the CCMA study design has been reported elsewhere [Holtzer et al., in press]. Briefly, older adults (>65 years) residing in Yonkers, NY, were first contacted via mail then over the phone. During the phone interview, they provided verbal consent and completed a brief medical history questionnaire, life space assessment [Harada et al., 2010], AD8 Dementia Screening Interview [Galvin et al., 2005], and the MIS. General exclusion criteria included severe auditory or visual loss, recent hospitalization that affects mobility, living in a nursing home, serious chronic or acute illness (e.g. cancer), and presence of dementia or other neurodegenerative disease.

Participants were then invited for two study visits. The first visit included written informed consent, demographic questionnaires, sensory screening, quantitative gait assessment, and comprehensive neuropsychological assessment. The second visit included medical, neurological, psychological, and motor assessments. Written informed consent was approved by the Albert Einstein College of Medicine Committee on Clinical Investigations. Upon the completion of the second study visit, a sub-set (33 out of the 450 CCMA participants) of interested participants was recruited for this experiment, which involved MRI scanning. Specific MRI exclusion criteria included left-handedness [Oldfield, 1971], claustrophobia, surgically implanted metallic devices (e.g. pacemaker) and presence of neurological gait disorder (e.g. neuropathy [Verghese et al., 2006]).

Procedure

After completing the VVIQ [Marks, 1973, 1995], each participant walked on a 4 × 14 feet course, recited alternate letters of the alphabet out loud while standing still, and walked the same 4 × 14 feet course while reciting alternate letters of the alphabet out loud. They were then trained to iW this course, imagine talking (iT: reciting alternate letters of the alphabet out loud) and iWWT this course. Prior to imagery training, they were also instructed to close their eyes during imagery, use both visual and kinesthetic imagery, and pay equal attention to both tasks in the iWWT condition. Seated at a desk, they then completed two trials of imagery training in 16-seconds blocks for approximately 15 min. Imagery instructions were presented auditorily and the beginning and the end of a block was initiated with a tone. During the first trial, instructions were detailed (e.g. "Imagine Walking: At the start of the next tone, close your eyes and imagine or envision yourself walking on the mat. At the start of the following tone, stop, and wait for further instructions"), but during the second trial they were simply prompted to begin at the start of the tone (e.g. "Imagine Walking"). Following each trial, participants were asked to evaluate the quality of their visual and kinesthetic images on the same 1 to 5 scale as the VVIQ (for a maximum total score of 10 points and a maximum mean score of 5 for visual imagery and kinesthetic imagery, respectively). They were then transported to the Gruss Magnetic Resonance Research Center (at Albert Einstein College of Medicine) situated two city blocks away from our center, and completed other cognitive tasks (unrelated to the predictions of this Experiment) in the MRI for approximately 15 min before the beginning of the imagery task. Imagery prompts were presented auditorily (and volume adjusted to ensure instructions could be heard clearly in the presence of scanning noise) and imagery occurred in 16-sec blocks (eyes closed). A tone indicated the beginning and the end of a block, and each block was repeated six times. Following the imagery task, participants were again asked to evaluate the overall quality of their visual and kinesthetic images on a 1 to 5 scale (for a maximum total and mean score of 5 points for visual and kinesthetic imagery, respectively).

MRI data acquisition and analysis

MRI scanning was performed with a Philips 3T Achieva Quasar TX multinuclear MRI/MRS system equipped with a Dual Quasar High Performance Gradient System, 32-channel broadband digital RF system, Quadrature T/R Head Coil, RapidView reconstructor, Intera Achieva ScanTools Pro R2.5 Package, NetForum and ExamCards, and SENSE parallel imaging capability. All BOLD (T2*-weighted) images [Kwong et al., 1992; Ogawa et al., 1993] were acquired with echo planar imaging (EPI) using a whole brain gradient over a 240 mm field of view (FOV) on a 128 × 128 acquisition matrix, 3 mm slice thickness (no gap); TE = 30 ms, TR = 2,000 ms, flip angle = 90 degrees, and 42 trans-axial slices per volume. A T1-weighted whole head structural image was also acquired using axial 3D-MP-RAGE parameters over a 240 mm FOV and 1.0 mm isotropic resolution, TE = 4.6 ms, TR = 9.9 ms, $\alpha = 8o$, with SENSE factor 2.5. The imagery task was written in E-Prime 2.0 (Psychology Software Tools Inc.) and presented with an InVivo Eloquence fMRI system.

Preprocessing

Image preprocessing were performed with SPM8 (Wellcome Department of Cognitive Neurology) implemented with MATLAB R2011b (Mathworks, Natick, MA). Each participant's EPI data set was realigned to the first volume to correct for motion, temporally shifted to correct for the order of slice acquisition, co-registered to the T1-weighted (structural) image, and spatially normalized [Friston et al., 1995] into Montreal Neurologic Institute (MNI) space using an older adult brain template supplied by the Clinical Toolbox [Rorden et al., 2012]. Finally, images were spatially smoothed with an isotropic Gaussian kernel, full-width-at half-maximum = 6 mm.

First-level analysis

The fMRI data time-series analyses consisted of two levels of voxel-wise General Linear Models (GLMs) [Friston et al., 1994; Holmes and Friston, 1998]. The first-level GLM yielded the contrast maps used in the second-level group analyses, which permits statistical inference at the population level. In the first-level GLM, the EPI time series were modeled with regressors that represented the expected BOLD response (implicitly relative to blanks) for each imagery condition (iW, iT, and iWWT). Each block was convolved with a canonical model of the hemodynamic response function supplied with SPM8. The contrast maps for iW, iT, and iWWT generated in our first-level analyses were then used in the second-level group covariance analyses.

Group-level covariance analysis

A Multivariate OrT Covariance Analysis (OrT-CVA) was implemented with the principal components analysis suite, which can be downloaded at http://www.nitrc.org/projects/gcva_pca [Gazes et al., 2012; Habeck and Stern, 2007; Habeck et al., 2005]. OrT-CVA was used to identify covariance patterns in the fMRI signal as a function of imagery task difficulty (iW, iT, and iWWT), and is similar to other covariance analyses such as partial least squares [McIntosh et al., 1996; Worsley et al., 1997] in that it employs a principal components analysis (PCA) to the data matrix that is then transformed to a matrix of the experimental design. The OrT-CVA design matrix is specifically sensitive to detecting variance that is consistent across participants and experimental conditions [Habeck et al., 2005]. Linear regression is then applied to detect a covariance pattern, or ordinal trend, in the fMRI signal as a function of imagery task condition that is based on a linear combination of a small set of principal components. An ordinal trend is a monotonic change in pattern expression as a function of task conditions. The expression of an ordinal trend is quantified in terms of a participant-specific expression score that is derived by projecting the covariance pattern onto a participant's scan for each task condition. These participant-specific (or pattern) expression scores can then be used for further analysis.

A permutation test was used to determine the statistical significance of the ordinal trend. The contrast images were re-sampled and the condition assignment broken while leaving the participant assignment intact. The re-sampled images were then submitted to OrT-CVA in order to derive a covariance pattern and compute the ordinal trend statistics [Habeck et al., 2005]. The ordinal trend statistic reflects the number of participants that fail to show a monotonic increase from iW to iT to iWWT. The permutation test was repeated 1,000 times to generate a null hypothesis histogram for the ordinal trend statistic and generate a P level that would correspond to the fraction of iterations that produced a statistic smaller than the point estimate value.

To determine the statistical significance of the stability of the voxel loadings of a covariance pattern we performed an additional nonparametric bootstrap test that, in contrast to the permutation test described earlier, maintained the condition assignment and resampled the data with re-placement. This process approximates the natural variation incurred from sampling the underlying distribution. A covariance pattern was then derived and applied to the resampled data, and a Z value computed: Z = point estimate/SD. Where the point-estimate was the voxel loading for the covariance pattern from the entire sample and the standard deviation was the variability from the bootstrap results around this point estimate. The resulting Z-map was thresholded at $Z > 1.96$, $P < 0.05$ (two-tailed) with a cluster threshold of 50 voxels. The anatomical labels for the cluster maxima in the covariance pattern were first determined using the Tailarach Client [Lancaster et al., 1997, 2000] and the probabilistic atlas of the human cerebellum [Diedrichsen et al., 2009, 2011] based on Schmahmann's cerebellar terminology [Schmahmann et al., 1999] and supplied by the Anatomy Toolbox [Eickhoff et al., 2005, 2006, 2007]. The assigned anatomical structures were then confirmed through visual inspection.

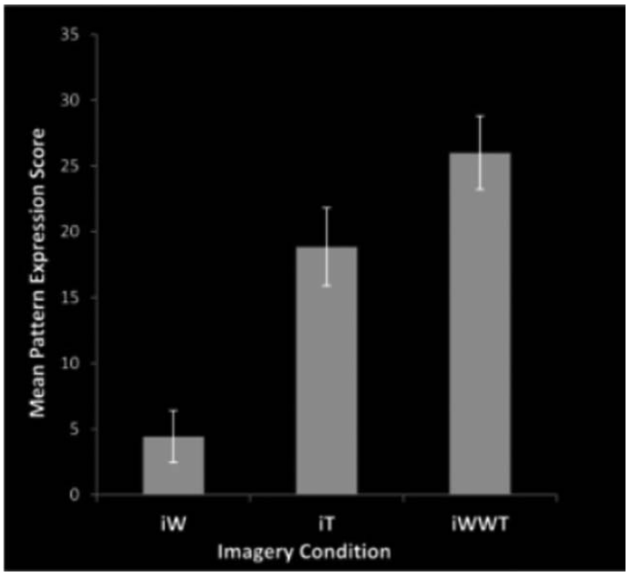

Figure 2.

Pattern expression scores as a function of imagery task difficulty in Experiment 2.

The participant-specific pattern expression scores were then correlated with age and visual and kinesthetic imagery ratings on the VVIQ, following imagery training, and upon the completion of the imagery task in the fMRI. These pattern expression scores were also correlated with gait velocity (cm/s) and cognitive performance (percent of correct letters provided; (correct/error x correct) × 100) during actual W, T and WWT. We also repeated these correlational analyses for participants with poor dual-task performance (the lowest tertile, ~33%) and strong dual-task performance (upper tertiles: ~66%), separately. Correlational analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics 20.0) and were thresholded at $P < 0.05$, two-tailed. Pearson's r were computed for all variables, except for the percent of correct letters during actual T and WWT, which were not normally distributed, and therefore Spearman's [*rho*] were computed instead.

RESULTS

The OrT-CVA analysis revealed a covariance pattern whose expression varied as a function of imagery task difficulty, $P < 0.001$ with four exceptions out of the 33 participants that did not follow the ordinal trend (see

TABLE II. Brain regions with positive and negative pattern weights

Cluster #	Region	Hem	BA	*x*	*y*	*z*	*z*-Value	*k*
Positive	Cerebellum (lobule VIIa, crus 1)	R/L	N/A	30	−67	29	6.16	879
	Precuneus	R	19	30	−64	40	5.70	603
	Precuneus	R	19	−30	−67	40	5.56	705
	Superior frontal gyrus (SMA)	R	6	6	14	49	4.89	1208
	Thalamus (ventral lateral nucleus)	L	N/A	−15	−13	13	4.21	454
	Middle frontal gyrus	R	10	39	35	25	3.62	74
	Thalamus	R	N/A	9	−10	10	3.61	112
	Insula	R	13	39	14	−2	3.48	79
	Inferior frontal gyrus (precentral gyrus)	R	9	42	8	34	3.30	97
Negative	Inferior occipital gyrus (lingual gyrus)	R	19	42	−70	−8	−5.05	2313
	Medial frontal gyrus	L	10	−6	47	−5	−4.53	123
	Middle temporal gyrus (angular gyrus)	L	39	−45	−61	22	−4.30	1089
	Insula	L	13	−36	2	20	−4.21	169
	Cingulate gyrus	L	24	−9	−19	43	−3.97	227
	Middle frontal gyrus	L	8	−30	14	37	−3.59	444
	Posterior cingulate	L	23	−6	−55	13	−3.36	251
	Postcentral gyrus	L	3	−39	−25	58	−3.25	56
	Inferior frontal gyrus	R	45	48	26	7	−3.03	55

Fig. 2 and Table II). Positive pattern weights are regions whose activation increased as a function of task difficulty (iW < iT < iWWT) and negative pattern weights are regions whose activation decreased as a function of task difficulty (iW > iT > iWWT). Regions with positive pattern weights that exceeded our threshold included bilateral cerebellum (Lobule VIIa; Crus I), bilateral precuneus, and several prefrontal cortex regions (superior frontal gyrus/SMA, middle frontal gyrus, and inferior frontal gyrus/precentral gyrus), as well as bilateral thalamus and

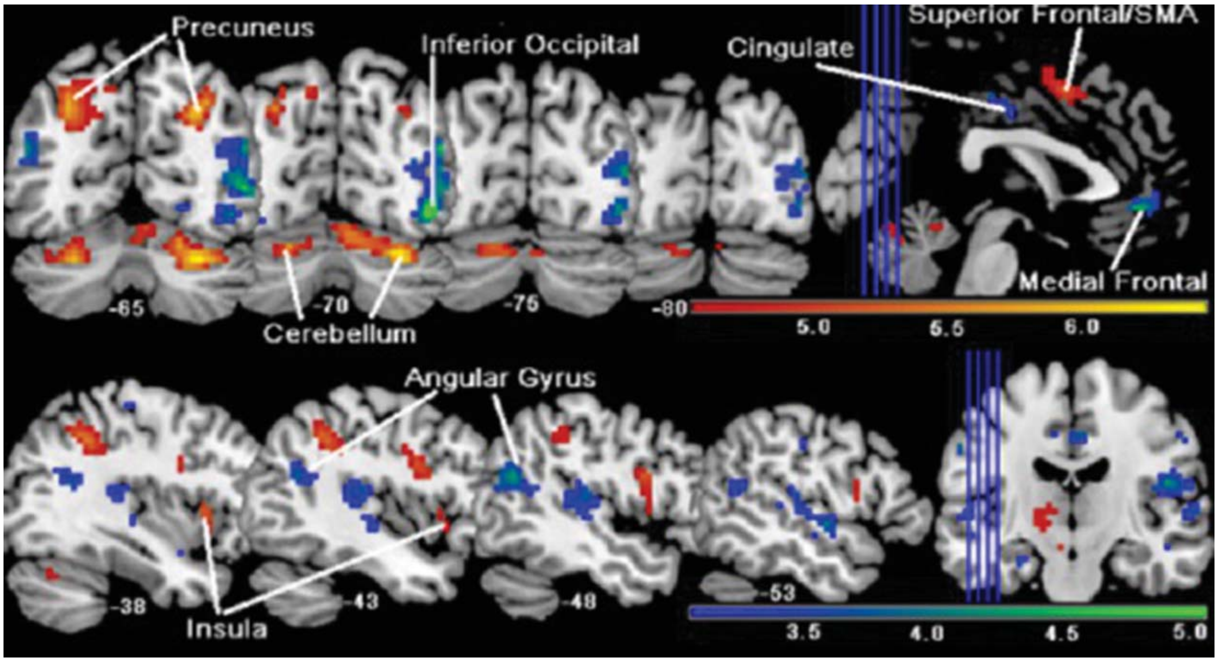

Figure 3.

Brain regions that increase and decrease as a function of task difficulty in Experiment 2. Brain regions that increase as a function of task difficulty (iWWT > iT > iW) are displayed in red-yellow and brain regions that decrease as a function of task difficulty (iWWT < iT < iW) are displayed in blue-green.

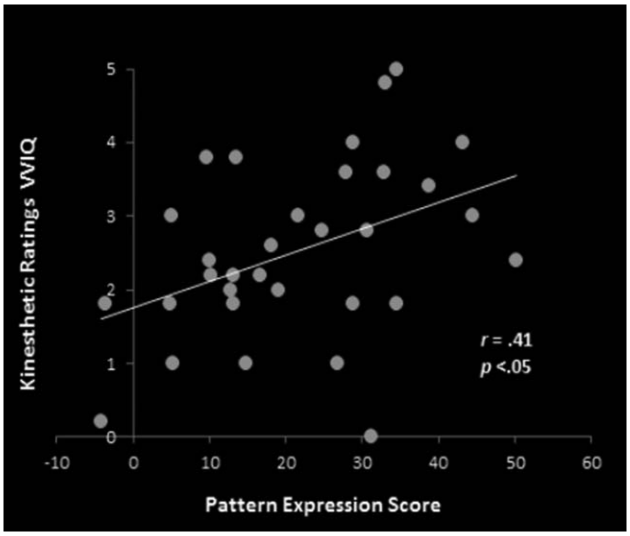

Figure 4.
The correlation between pattern expression scores and kinesthetic imagery ratings on the VVIQ in Experiment 2.

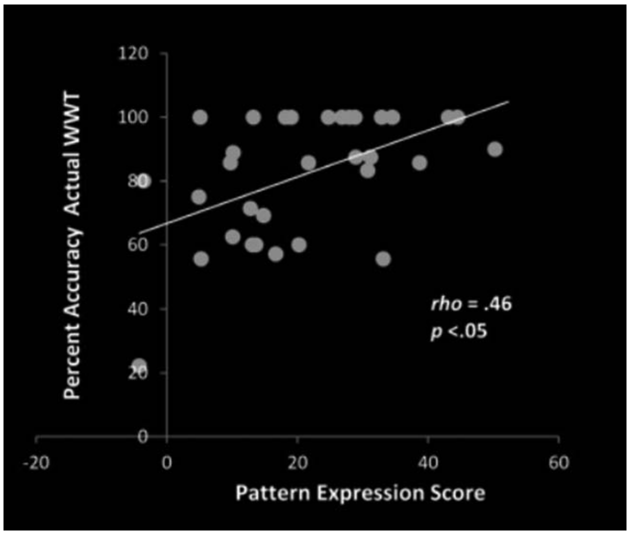

Figure 6.
The correlation between pattern expression scores and percent accuracy during actual Walking-While Talking in Experiment 2.

right insula (see Fig. 3 and upper panel of Table II). Regions with negative pattern weights that exceeded our threshold included right inferior occipital gyrus (including lingual gyrus), left middle temporal gyrus, and left medial frontal gyrus, as well as left cingulate gyrus and left posterior cingulate and left insula (see Fig. 3 and lower panel of Table II).

The expression of this covariance pattern that varied as a function of task difficulty did not vary as a function of age; however, it was associated with kinesthetic imagery ratings and cognitive performance during actual WWT[1]. More specifically, kinesthetic imagery ratings on the VVIQ and following imagery training were positively correlated with the increase in pattern expression from iW to iWWT, $r = 0.41$, $P < 0.05$ (see Fig. 4) and $r = 0.43$, $P < 0.05$ (see Fig. 5), respectively. This increase in pattern expression was also positively correlated with the percent correct letters that were provided during actual WWT, $[rho] = 0.46$, $P < 0.05$ (see Fig. 6). This increase in pattern expression did not correlate with visual imagery ratings on the VVIQ, following imagery training, or upon the completion of the imagery task in the fMRI. This increase in pattern expression was also not associated with kinesthetic imagery ratings upon the completion of the imagery task in the fMRI, gait velocity during actual W and WWT, or cognitive performance during actual T.

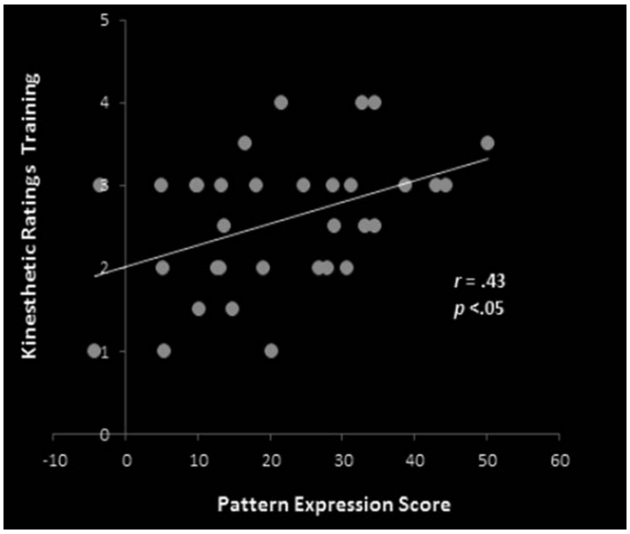

Figure 5.
The correlation between pattern expression scores and kinesthetic imagery ratings following imagery training in Experiment 2.

Finally, among older adults with poor dual-task performance, the expression of this covariance pattern that varied as a function of task difficulty was positively correlated with visual ($r = 0.78$, $P < 0.001$) and kinesthetic ($r = 0.91$, $P < 0.001$) imagery ratings on the VVIQ, visual ($r = 0.69$, $P < 0.05$) and kinesthetic ($r = 0.73$, $P < 0.05$) imagery ratings following imagery training, and cognitive performance during actual WWT ($[rho] = 0.72$, $P < 0.05$). Among older adults with strong dual-task performance, however, the expression of this covariance patent was only negatively correlated with visual imagery ratings following imagery training ($r = 0.54$, $P < 0.01$).

DISCUSSION

Very little is known about the behavioral and neural correlates of imagined gait in the elderly, particularly in a dual-task situation such as iWWT. In fact, to our knowledge, no study has examined the behavioral or neural correlates of imagined gait in a dual-task situation previously. The key findings from the current study are: (1) real and imagined walking and walking-while-talking times are highly correlated, (2) a pattern of brain regions co-vary as a function of the difficulty of the imagined gait task, and (3) the expression of this covariance pattern is associated with imagery ratings and cognitive performance during actual WWT. We discuss each of these three key findings in turn.

Real and Imagined Walking and Walking-While-Talking Times are Highly Correlated

The close temporal correspondence between real and imagined W and WWT times observed in the current study validates our measure and assures us that older adults can be trained to accurately imagine complex gait performance. Yet, keeping in mind that dual-task costs were greater during the imagined than the real version of the task, indicating that the imagined version of the task could be more demanding. There are two fundamental implications of this key finding.

First, it establishes feasibility for developing rehabilitative tools that involve motor imagery in dual-task situations that are particularly challenging to the elderly, and stronger predictors than normal pace walking of adverse outcomes such as falls [Verghese et al., 2002a]. As mentioned in the Introduction, motor imagery is a proven rehabilitative tool for Parkinson's disease [Heremans et al., 2011; Tamir et al., 2007] and post stroke [Dunsky et al., 2008; Kim et al., 2011; Verma et al., 2011], and gait decline is associated with increased risk for future cognitive decline and dementia [Marquis et al., 2002; Verghese et al., 2007b; Waite et al., 2005; Wang et al., 2006]. Hence, the imagined W and WWT task employed in the current study could potentially be a useful rehabilitative tool for improving gait and cognition in aging, and or for preventing gait decline, cognitive decline, and dementia [Schwenk et al., 2010; Verghese and Holtzer, 2010]—although these cross-sectional findings need to be confirmed and extended in longitudinal studies and different aging populations. Future studies are also needed to determine when and how much training is required (or ideal) for accurately performing complex imagined gait tasks. In the current study of cognitively-healthy older adults, we observed strong correlations between real and imagined W and WWT after a single session of practice, but it is possible that additional training would (a) strengthen these correlations further, (b) positively influence subsequent gait and cognition, and (c) be necessary in clinical populations such as older adults with neurological gait abnormalities.

In contrast to a recent study [Bridenbaugh et al., 2013] that found a poor correlation between the real and the imagined versions of the get up and go task [Beauchet et al., 2010, 2011] among older adults with poor dual-task performance, however, we found a stronger correlation between real and imagined W and WWT among those with poor dual-task performance compared with those with strong dual-task performance. The discrepancy between these findings could be the result of different task demands (e.g. the get up and go task has no cognitive load) and or study samples (older adults with gait disorders, falls or memory problems vs. cognitively-healthy older adults). Direct comparisons of these tasks in the same study sample would be particularly informative for the future development of interventions that involve imagined gait.

Second, the temporal correspondence between real and imagined W and WWT assures us that this paradigm can be used to examine the neural correlates of complex gait performance with fMRI. As mentioned in the Introduction, a fairly recent study using [^{18}F] FDG-PET suggests that supplementary, rather than primary, motor cortices are activated during imagined gait [la Fougere et al., 2010]. A recent meta-analysis of neuroimaging studies of imagery further suggests that the absence or a reduction in primary sensory and motor engagement is a good rule of thumb for the neural systems involved in imagery versus real perception or action in general [McNorgan, 2012]. This meta-analysis also suggests that different forms of imagery including, but not limited to, visual, auditory, tactile and motor imagery, do not engage primary sensory and motor cortices as much as the actual perception or action. The results of this meta-analysis also suggest that a general imagery network that is mostly left-lateralized, and includes the superior parietal lobule, precuneus, inferior frontal gyrus and the middle occipital gyrus, is consistently engaged during different forms of imagery. Unlike the majority of fMRI studies of imagined gait, which typically contrasts imagined gait with imagined standing or lying [Cremers et al., 2012; Jahn et al., 2004, 2008], we examined the neural systems involved in a dual-task that involves coordinating imagined gait and cognition. This issue has not been previously explored, but is critical to examine in older adults, who are particularly impaired in dual-task situations.

A Pattern of Brain Regions Co-Vary as a Function of the Difficulty of the Imagery Task

A multivariate OrT-CVA identified a pattern of brain regions that varied as a function of imagery task difficulty, and consisted of both positive (increases; $\text{iW} < \text{iT} < \text{iWWT}$) and negative (decreases; $\text{iW} > \text{iT} > \text{iWWT}$) components. Increases as a function of task difficulty were observed mostly in bilateral cerebellum (Lobules VIIa and Crus I), bilateral precuneus and prefrontal cortex (right superior frontal gyrus/SMA, middle frontal gyrus, and inferior frontal gyrus/precentral) regions. Decreases as a function of task difficulty were observed mostly in right inferior occipital (extending into middle occipital and lingual gyrus), left middle temporal (extending into angular gyrus), and left cingulate regions.

Increases in prefrontal cortex activation as a function of imagery task difficulty is consistent with our previous finding of increased prefrontal activation during actual Walking-While-Talking compared with Walking as measured with functional Near Infrared Spectroscopy or fNIRS [Holtzer et al., 2011]. fNIRS is a noninvasive imaging technique that permits one to image the brain during locomotion, but is limited to examination of the neural correlates of gait that are close (~2.5 cm) to the surface of the skull (e.g. the prefrontal cortex). In that study, both younger and older adults engaged prefrontal cortex regions to a greater extent when they were asked to walk while reciting alternate letters of the alphabet (WWT) compared with when they were asked to walk alone (W). Moreover, the blood oxygenation increases associated with WWT relative to W in these prefrontal cortex regions were bilateral, and present in both younger and older adults.

Increases in prefrontal cortex activation as a function of imagery task difficulty also confirms the suggestion that the allocation of attention between imagined gait and cognition indeed engages prefrontal cortex regions that have been repeatedly linked to executive functions, and are known to be particularly affected in aging. The right middle frontal and precentral gyrus has also consistently been linked to motor imagery, and the inferior frontal gyrus (although primarily left-lateralized) is one of the primary components of the recently proposed modality-general imagery network [McNorgan, 2012]. Taken together, these prefrontal increases suggest that the iWWT task adapted for the current study engages executive functions and taps into similar neural systems as actual WWT, motor imagery, and other forms mental imagery.

Future use of this paradigm in studies that contrasts younger and older adults, will speak to the issue of whether older adults overutilize or underutilize these prefrontal cortex regions during iWWT. Future studies, examining real and imagined WWT as a function of training or practice, will speak to the issue of whether older adults can be trained to recruit prefrontal cortex regions to the same extent as younger adults while performing this task, and/or learn to recruit brain regions that may be less affected by aging [Stern et al., 2005, 2012]. Finally, future intervention studies will speak to the issue of whether this imagined gait protocol can be used to optimize prefrontal cortex engagement and transfer to, or improve, mobility and cognitive functions in older adults.

Increases in cerebellar activation as a function of increasing imagery task difficulty is consistent with previous fMRI findings of imagined gait [Cremers et al., 2012; Jahn et al., 2004, 2008; van der Meulen et al., in press; Zwergal et al., 2012] and, more importantly, extends them to a dual-task that demands additional executive functions. The cerebellum has been extensively linked to the control of movement, but a growing body of evidence now suggest that the cerebellum plays an integral role in executive functions as well [Leiner et al., 1986; Stoodley, 2012; Stoodley and Schmahmann, 2009]. Initially, motor functions were attributed to the anterior portion of the cerebellum while executive functions were attributed to the posterior portion of the cerebellum [Schmahmann and Sherman, 1998]. A recent review and a meta-analysis of fMRI studies of cerebellar engagement, however, more specifically attribute motor functions to lobules I-V, and lobule VIII, and executive functions to Lobules VI, VII, VIIa VIIb, Crus I and Crus II [Stoodley, 2012; Stoodley and Schmahmann, 2009]. Thus, the increased activation observed in Lobules VIIa/Crus I as a function of imagery task difficulty are consistent with the suggestion that complex gait performance such as iWWT necessitates additional executive functions. This suggestion is also consistent with recent resting-state fMRI studies (often considered to reflect underlying anatomical connections) that have shown that while activity in lobules V, VI, and VIII correlates with activation in sensory, motor and pre-motor cortices, activity in Lobules VIIa, Crus I, and Crus II correlates with activation in prefrontal and posterior-parietal cortices [Habas et al., 2009; Krienen and Buckner, 2009; O'Reilly et al., 2010]. Thus, the cerebellar increases observed as a function of task difficulty in this study are consistent with previous imagined gait studies, and further supports the suggestion that iWWT demands a considerable amount of executive functions.

Increases in precuneus activation as a function of increasing imagery task difficulty is also consistent previous fMRI studies of imagined gait [Cremers et al., 2012; Jahn et al., 2004, 2008; Zwergal et al., 2012], and extends them to a dual-task situation. Interestingly, increased activation in the precuneus has also been observed when contrasting more complex imagined gait tasks such as imagined walking with obstacles to less complex imagined gait tasks such as walking alone [Malouin et al., 2003; Wang et al., 2009]). Like iWWT, imagined walking with obstacles presumably demand more executive functions than walking alone. The precuneus has also been linked to a number of different higher-order cognitive functions, including mental imagery of the self and episodic memory retrieval; for a review see Cavanna and Trimble [2006]. Like the cerebellum, the precuneus is anatomically connected to the prefrontal cortex. It is also one of the primary components of the recently proposed modality-general imagery network [McNorgan, 2012]. In other words, the precuneus increases observed as a function of task difficulty in this study are consistent with previous imagined gait studies, particularly those that employ more complex imagined gait tasks.

The decreases observed in occipital, middle temporal, medial frontal and cingulate regions as a function of imagery task difficulty are difficult to interpret in the context of previous imagined gait studies, which typically use traditional univariate analyses aimed at revealing increases (rather than decreases in activation) during imagined gait relative to imagined lying or standing [Cremers et al., 2012; Jahn et al., 2004, 2008; van der Meulen et al., in press; Zwergal et al., 2012]. Decreases in middle temporal, medial frontal gyrus and cingulate regions, as a function of dual-task demands, however, have been previously observed in younger and older adults using an OrT covariance-based analytic approach [Gazes et al., 2012]. This study did not involve imagined gait, but examined neural activation associated with dual-task costs when participants performed vowel-consonant and or lower-upper case letter judgements. Thus, it is possible that these decreases are associated with moving from a single to a dual-task regardless of whether the dual-task involves imagery or does not involve imagery—an intriguing hypothesis that could be systematically tested in future studies.

Decreases in occipital activation as a function of task difficulty have also been reported previously during a nonverbal (shape) delayed item recognition task, using a similar covariance-based analytic approach [Blumen et al., 2011; Holtzer et al., 2004, 2009; Stern et al., 2012]. These studies also did not involve imagined gait and manipulated task difficulty by varying working memory set size (1 to 3; [Holtzer et al., 2009]) or by varying response deadlines (125 ms to 2,000 ms (Blumen et al., 2011; Stern et al., 2012]). More specifically, these studies reported decreased occipital (lingual gyrus) activation as a function of increasing set size [Holtzer et al., 2009] and decreasing response deadlines [Blumen et al., 2011; Stern et al., 2012]. Thus, it is possible that the decreases in occipital cortex activation as a function of imagery task condition that were observed in the current study are not specific to imagery or dual-tasks, but are associated with increasing task difficulty in general.

The Covariance Pattern That Varied as a Function of Task Difficulty is Associated With Imagery Ratings and Cognitive Performance During Actual WWT

Overall, the covariance pattern of increasing and decreasing neural activation as a function imagery task difficulty was positively associated with kinesthetic imagery ratings, but not visual imagery ratings. In other words, older adults expressed this pattern to a greater extent if they provided greater kinesthetic imagery ratings, and vice versa. The fact that cerebellar (VIIa and Crus I) and cingulate regions were positive components of this covariance pattern is consistent with a previous study reporting cerebellar (Lobule VI, VII, and Cruz I) and cingulate cortex activity when individuals were instructed to focus on the kinesthetic aspects of finger movements compared with when they were instructed to focus on the visual aspects of finger movements [Guillot et al., 2009]. The same researchers also reported decreased occipital activation when instructed to focus on the kinesthetic aspects of finger movements compared with the visual aspects of finger movements, which is also consistent with our findings.

Overall, the covariance pattern of increasing and decreasing neural activation varied as a function of imagery task difficulty was also associated with cognitive performance (accurate letters provided), but not with gait velocity during actual WWT. This finding suggests that this covariance pattern is associated with the cognitive components of imagined WWT rather than the motor components of imagined WWT—and implies that participants had to allocate more attention to the cognitive task in the dual-task imagery condition. Past research has shown that when younger and older adults are instructed to prioritize the cognitive task during actual WWT [Verghese et al., 2007a] their gait velocity is reduced, but their cognitive performance remain unchanged. In the current study, we instructed participants to pay equal attention to both task, but it is possible that as task difficulty increased, they emphasized alternate letter generation. It is also possible that increasing task difficulty in general made the cognitive task more challenging. These initial findings are intriguing and future research that explicitly manipulates task prioritization during iWWT will shed further light on this issue.

Interestingly, the covariance pattern of increasing and decreasing neural activation that varied as a function of imagery task difficulty correlated differently with imagery ratings and cognitive accuracy in older adults with poor dual-task performance compared with strong dual-task performance. Among older adults with poor dual-task performance, the covariance pattern of increasing and decreasing neural activation as a function imagery task difficulty was positively associated with visual and kinesthetic imagery ratings and cognitive performance, but this was not the case among older adults with strong dual-task performance. In fact, among older adults with strong dual-task performance, our covariance pattern was only negatively associated with visual imagery ratings. These individual differences suggest that the overall correlations between pattern expression scores, kinesthetic imagery and cognitive accuracy were primarily driven by older adults that have more difficulty with dual-task performance, and that an overall correlation with visual imagery ratings were disguised by the opposing pattern of correlations in older adults with strong dual-task performance.

CONCLUSIONS

The current study examined the behavioral and neural correlates of imagined gait in aging with a new imagined gait protocol that involves a dual-task situation, which demands executive functions and is particularly challenging to older adults—presumably because it engages prefrontal regions that a particularly affected in aging. There was a close temporal correspondence between real and imagined W and WWT. Activation in prefrontal cortex regions, as well as cerebellar and precuneus regions that are anatomically connected to the prefrontal cortex, also increased as a function of task difficulty (iW < iT < iWWT), and correlated with kinesthetic imagery ratings and cognitive performance during actual WWT. These initial findings suggest that the executive, kinesthetic and cognitive components of the human locomotion system increase as a function of imagined gait task difficulty, and are encouraging for future research and development of interventions that involve imagined gait in dual-task situations.

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