NeuroImage 189 (2019) 551–559

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Age-related changes in attention control and their relationship with gait performance in older adults with high risk of falls

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ARTICLE INFO

Keywords:
Aging
Fall risks
Gait
Neuroimaging
Cognitive aging

ABSTRACT

Background: Falls are the leading cause of injury-related deaths in the elderly worldwide. Both gait impairment and cognitive decline have been shown to constitute major fall risk factors. However, further investigations are required to establish a more precise link between the influence of age on brain systems mediating executive cognitive functions and their relationship with gait disturbances, and thus help define novel markers and better guide remediation strategies to prevent falls.
Methods: Event-related functional magnetic resonance imaging (fMRI) was used to evaluate age-related effects on the recruitment of executive control brain network in selective attention task, as measured with a flanker paradigm. Brain activation patterns were compared between twenty young (21 years $\pm$ 2.5) and thirty-four old participants (72 years $\pm$ 5.3) with high fall risks. We then determined to what extend age-related differences in activation patterns were associated with alterations in several gait parameters, measured with electronic devices providing a precise quantitative evaluation of gait, as well as with alterations in several aspects of cognitive and physical abilities.
Results: We found that both young and old participants recruited a distributed fronto-parietal-occipital network during interference by incongruent distractors in the flanker task. However, additional activations were observed in posterior parieto-occipital areas in the older relative to the younger participants. Furthermore, a differential recruitment of both the left dorsal parieto-occipital sulcus and precuneus was significantly correlated with higher gait variability. Besides, decreased activation in the right cerebellum was found in the older with poorer cognitive processing speed scores.
Conclusions: Overall results converge to indicate greater sensitivity to attention interference and heightened recruitment of cortical executive control systems in the elderly with fall risks. Critically, this change was associated with selective increases in gait variability indices, linking attentional control with gait performance in elderly with high risks of falls.

1. Introduction

Occurring at least once a year for one-third of the community-dwelling adults over the age of 65, falls are common geriatric events playing a major role in injury-related deaths in the elderly (Tinetti et al., 1988). Falls are associated with gait impairments that become more frequent with increasing age, such as walking speed reduction or walking irregularity. The prevalence of these gait changes ranges from 10% around 60 years old to 60% in individuals older than 80 years old (Pirker and Katzenschlager, 2017). Gait impairments may contribute to a loss of independence and limitations in everyday activities, but also constitute a reliable predictor of fall risk in the elderly community (Montero-Odasso et al., 2005). It is therefore crucial to better understand the mechanisms underlying changes in gait stability and risks for falls, which are one of the top public health and economical concern in our aging society.

Among the numerous age-associated changes, impairments in the gait pattern, reduced balance, lower muscle strength, as well as decline in cognitive abilities have been identified as independent predictors of falls in the elderly (Ambrose et al., 2013). Several studies also reported a frequent coexistence of these main fall-risks factors and highlighted in particular an important relationship between gait disturbances and cognitive difficulties, notably a relative decline in executive functions

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https://doi.org/10.1016/j.neuroimage.2019.01.030
Received 1 August 2018; Received in revised form 28 December 2018; Accepted 11 January 2019
Available online 18 January 2019
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and multitasking abilities (i.e., divided-attention) (for a review, see Paraskevoudi et al., 2018). Thus, both gait disturbances and poor executive control performance are more prevalent in older adults with higher risks of fall (Montero-Odasso et al., 2012; Kearney et al., 2013), and both were prospectively related to later fall events (Herman et al., 2010). These findings suggest that executive control abilities, essential to process goal-relevant stimuli and ignore distracting information in order to efficiently guide behaviour in daily living activities, might be an important element in maintaining efficient locomotion, whereas conversely decline in executive control may contribute to impairments in gait characteristics and subsequent increases in fall occurrences in the aging population. However, the neural substrates implicated in such interplay between gait impairments and cognitive functions, particularly executive control, remain poorly understood.

Age-related alterations in executive control are relatively well-established across various studies and tasks. Performance is particularly reduced in attentional conflict paradigms, for instance the Eriksen flanker task that involves both selective attention and response conflict resolution (Hasher et al., 2007; Zhu et al., 2010). In the flanker task, target stimuli requiring a particular response are presented together with distractors associated with either the same or another response (congruent or incongruent trials, respectively). By comparing these two conditions, previous work demonstrated an increased sensitivity to distractors in the aging population, with slower performance, more frequent errors, and functional changes in several brain areas regulating executive control processes, relative to the younger adults. Accordingly, several neuroimaging studies reported over-recruitment of prefrontal and parietal cortices (Nielson et al., 2002; Huang et al., 2012), usually interpreted as neural compensatory mechanisms that could mitigate the cognitive decline related to increasing age (Cabeza, 2002).

However, less is known about how brain networks mediating executive control are functionally modified in individuals with gait impairments and higher fall risks. Differential recruitment of the executive control network has been reported in faller and non-faller elderly, but with an overall reduction of activations across the whole brain (Nagamatsu et al., 2013) or more specifically in the right-cerebellum during attentional tasks (Liu-Ambrose et al., 2008). Moreover, a majority of studies compared faller and non-faller populations whose definition was mainly based on the number of falls reported during a short observation period prior to the study, or through the Physiological Profile Assessment (PPA), a questionnaire assessing different dimensions of fall risks. However, these measures may be imprecise as they are based on subjective reports and memory retrieval, whose reliability may vary in aging population. Other measures offer more objective and robust predictors of less optimal aging associated with greater frailty and higher falls risk in these individuals. Notably, alterations in gait pattern have been found to be a reliable marker of fall risk in older adults (Hausdorff et al., 2005). Specifically, changes in spatio-temporal parameters and variability of the gait, as assessed using novel electronic devices (i.e., instrumented pressure-sensitive walkways), have been identified as independent predictors of future falls (Beauchet et al., 2017). These objective measures might therefore provide valuable indicators probing age-related changes in the brain that underlie difficulties in both cognitive processes (executive control) and physical capacity (i.e., gait and balance) in the elderly.

In the present study, we aimed to determine the effect of aging on executive control and their neural correlates by comparing older adults at high risk of falls and young adults who were tested on a similar Eriksen flanker task (Zhu et al., 2010) while they underwent brain scanning with fMRI. This task has been frequently used in studies of executive control in the elderly (Zhu et al., 2010; Korsch et al., 2013) and more particularly in fallers (Colcombe et al., 2004; Liu-Ambrose et al., 2008; Nagamatsu et al., 2013). Both behavioural and neural measures obtained during this task allowed us to directly examine the relationship between the influence of age on brain systems governing executive control processes and functional alterations in the elderly that have been related to increased fall risks, including changes in gait characteristics and relative declines in cognitive abilities. Based on previous work, we expected the elderly in general, and more particularly those with objective gait disturbances, to exhibit differential recruitment of the executive control network, encompassing both anterior brain areas associated with conflict processing (i.e., dorsolateral prefrontal cortex and dorsal anterior cingulate gyrus) and more posterior brain areas associated with top-down mechanisms of selective attention (i.e., parietal cortices). To this aim, we recruited a group of elderly individuals who were healthy (i.e. no neurological or rheumatologic disorder) but with demographic/clinical factors known to be associated with higher fall risk. We first performed a whole-brain fMRI analysis to identify between-group differences (old vs young) in activation patterns during conditions requiring executive control (flanker task), and then correlated these differences with behavioural scores measuring gait characteristics as well as cognitive and functional abilities.

2. Patients and methods

2.1. Participants

Twenty young (M = 21 years ± 2.5) and thirty-four community-dwelling older adults (M = 72 years ± 5.3), matched for education duration (M = 14 years), took part in our study. Because of a large discrepancy of gender among older volunteers who responded to recruitment adverts, only female participants were included in the final sample of our study (both the controls and elderly). All participants were French speakers, right-handed (determined with the Edinburgh Handedness Inventory), had normal or corrected-to-normal vision, and no history of neurological/psychiatric/toxicological disease. Older adults presented no history of any mental, neurological, musculoskeletal or rheumatologic disease, and were included if they met at least one of the following vulnerability criteria for risk falls: (i) one or more self-reported fall events after the age of 65; (ii) balance impairment as assessed by a simplified Tinetti Gait & Balance test (TT; Tinetti et al., 1988) with a score higher than 2 out of 7; or (iii) one or two criteria for physical frailty (Fried et al., 2001). These participants were recruited from a large sample investigated for risks of fall in the context of an ongoing clinical randomized cohort study. All of them gave detailed information about their medical history, including the number of falls and injuries experienced in the past 12 months, their usual activity level, and any current or recent medications. Of note, older participants were excluded if their medical history or physical examination revealed any condition (e.g., neurological, neuromuscular, orthopaedic, including severe arthritis or pain) that could have a significant impact on their gait and/or balance and would thus compromise physical outcomes assessment. All participants gave informed consent in accordance with regulation of the ethic committee at the University Hospital of Geneva.

2.2. Clinical scores assessment

All clinical scores for cognitive and gait performance were measured in the older adult group only. These scores are presented in Table 1, in the result section. Several classic neuropsychological tests were performed in the older adult group to assess different aspects of interest of related to cognitive control. Frontal lobe functions were evaluated using the Frontal Assessment Battery (FAB) (Dubois et al., 2000), while memory and processing speed were assessed using the Digit Symbol-Coding (DSC) subtest from the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997). The Mini-Mental State Examination (MMSE) evaluated global intellectual efficiency through six cognitive domains (Folstein et al., 1975).

Functional physical performance was measured using several tests widely used in older adults (detailed in supplementary material). The short version of the Tinetti Gait & Balance test was used to probe both gait and balance, while overall mobility capability was assessed with the Timed Up & Go test (TUG; Podsiadlo and Richardson, 1991). The Short

Table 1

Demographic information and clinical scores for the older group. Mean group values are presented with the standard deviation. Abbreviation: n = number of participants; y = years; nbr = number; % = percentage; cm/s = centimetres per second; ms = milliseconds; total = total score; CV = coefficient of variation; FAB = Frontal Assessment Battery; MMSE = Mini-Mental State Examination; DSC = Digit Symbol-Coding; TT = Tinetti Gait & Balance test; TUG = Timed Up & Go test; SPPB = Short Physical Performance Battery.

Participants Characteristics									
	Socio-Demographic characteristics			Cognitive assessment			Functional assessment		
	Age (y)	Education (y)	Falls (nbr)	FAB (total)	MMSE (total)	DSC (total)	TT (total)	TUG (ms)	SPPB (total)
Young adults (n = 20)	21.4 ± 2.5	13.9 ± 1.6	–	–	–	–	–	–	–
Older adults (n = 34)	72.7 ± 5.3	12.6 ± 2.2	1.1 ± 1.9	16.2 ± 1.4	27.6 ± 2.4	55.0 ± 13.0	0.4 ± 0.7	10.6 ± 1.7	10.0 ± 1.5
Spatio-Temporal gait measurement									
	Normal walking			Simple Dual-task walking			Complex Dual-task walking		
	Stride length CV (%)	Stride time CV (%)	Velocity (cm/s)	Stride length CV (%)	Stride time CV (%)	Velocity (cm/s)	Stride length CV (%)	Stride time CV (%)	Velocity (cm/s)
Older adults (n = 34)	2.8 ± 1.2	2.4 ± 1.4	110.5 ± 18.8	3.8 ± 2.1	4.9 ± 4.3	95.6 ± 24.0	5.3 ± 3.3	9.6 ± 8.8	74.3 ± 28.5

Physical Performance Battery (SPPB; Guralnik et al., 1994) evaluated three domains of physical function (i.e., balance, gait speed and lower-limb strength).

Finally, a quantitative spatio-temporal gait analysis was performed in the older group using an electronic pressure-sensitive walkway (GAITRite; CIR Systems Inc, Havertown, Pennsylvania, USA) (Hars et al., 2013). Both spatial and temporal gait variability (based on stride length and stride time, respectively) provide sensitive markers of fall risk (Hausdorff, 2005), and were quantified here by computing the coefficient of variation (CV = *[standard deviation/mean] x 100*) for each measure, expressed as a percentage. Additionally, we measured the velocity of gait (cm/seconds). All three gait parameters were recorded under simple (i.e., normal walking, NW) and dual-task conditions (i.e., dual-task walking, DW). The dual task involved a simple dual walking condition (SDW) in which participants had to count aloud backward by 1, starting from 50, and a complex dual walking condition (CDW) in which they counted backward by 3, starting from a random number (between 300 and 900). In all conditions, participants were asked to walk at their self-selected, usual walking speed. All spatio-temporal gait measurements obtained according to our procedure, with an average of 15 consecutive steps captured per gait condition, have been found to be reliable in older adults by our group (Hars et al., 2013), and have been used in previous interventional studies (Trombetti et al., 2013, Cullen et al., 2018). For more technical details related to the assessment of spatio-temporal gait characteristics, see supplementary material.

2.3. Executive control task

A modified Eriksen flanker task (Eriksen and Eriksen, 1974) involving selective attention and response conflict was used to recruit fronto-parietal networks mediating executive control. Visual stimuli consisted of a row of five horizontal arrows, with the centre arrow having either the same or the opposite direction than the other flanking arrows, referred as the *Congruent* condition (Con) and *Incongruent* condition (Inc), respectively. On each trial, this visual arrow display was presented for a fixed duration of 1700 ms, preceded by a fixation cross with a jittered duration of 2000–4000 ms (see Supplementary Figure 1). Participants had to report the direction (right or left) of the central arrowhead (target) as quickly and accurately as possible, by pressing the corresponding button on an MRI-compatible joystick device (Current Designs; Part number: HHSC-JOY-1). In addition, a *Baseline* condition, consisting of five horizontal white dashes instead of the arrows, was implemented to obtain baseline fMRI signal associated with non-specific visual effects. In this condition, participants were asked to simply look at the visual display without responding.

2.4. Behavioural data analysis

Both accuracy (AC; percentage of correct responses) and average reaction times (RT; in milliseconds) were calculated for each participant and each group (young and older adults) for both the congruent and incongruent conditions. Statistical analyses were performed using the R Software (R., R Development Core Team). Data were tested for normality of the residuals distribution and equality of variances. Based on these results, accuracy was analysed using non-parametric Wilcoxon tests to assess congruency and group effects. Additionally, the flanker cost (*[(mean AC* $_{Con}$*) minus (mean AC* $_{Inc}$*)]*) was calculated for each participant and compared between groups using an unpaired Wilcoxon test. Following a log transformation, RT were examined using a 2 × 2 mixed-model repeated-measure ANOVA with the two congruency conditions as a within-subject factor and group as a between-subject factor. Post-hoc analyses were performed using *t*-tests. We also computed the flanker RT cost (*[(mean RT* $_{Inc}$*) minus (mean RT* $_{Con}$*)]*), which was compared between groups using an unpaired Wilcoxon test.

Spearman Rank Correlations were performed in the elderly to test for the predicted associations between executive control (i.e., flanker RT cost) and the relevant clinical measures of age-related changes (i.e., cognitive, functional, and gait scores) plus history of falls. All p-values were adjusted with Bonferroni correction for multiple comparisons.

2.5. fMRI data acquisition and analysis

Brain imaging data were acquired in a 3T MRI scanner (Siemens TIM Trio, Germany) with a standard 12-channel head coil using a multi-slice echo-planar sequence in single shot for functional images (T_2*-weighted; TR/TE = 2000/30 ms, flip angle = 85°, Voxel dimensions = 3 mm isotropic, field of view [FOV] = 192 × 192 mm), and a magnetization-prepared rapid acquisition gradient echo sequence for structural images (T_1-weighted; TR/TE = 1900/2.27 ms, flip angle = 9°, Voxel dimensions = 1 mm isotropic, Matrix = 256 × 256).

All statistical analyses were performed using Statistical Parametric Mapping (SPM8, Wellcome Trust Centre for Imaging, London, Uk). Following standard image preprocessing (realignment, co-registration, slice-timing correction, 8 mm-kernel smoothing and normalization), the first-level analysis was done using a general linear model, to model all correct trials from the two experimental conditions (Con and Inc), plus trials of the baseline condition and a supplementary vector containing error trials. Trial onset was aligned on the visual target appearance (1700 ms duration), convolved with the canonical hemodynamic response function (cHRF). Additionally, the six realignment parameters were entered as covariates of no interest. Our use of a standard SPM cHRF for all participants accords with a recent study reporting no significant changes in the shape of the HRF and similar neurovascular coupling with increasing age (Grinband et al., 2017), and thus avoids any systematic bias in data processing between groups (see Supplementary Material for additional procedures concerning age-related effects). T-contrasts were computed at the first-level to compare the two congruency conditions with each other and with the Baseline condition (Bas) for each individual.

A second-level group analysis was then performed using a flexible factorial design, where task conditions (baseline, congruent, and incongruent trials), group (older and young), and subject were considered as separate factors. First, the main effect of executive control (attentional conflict), was determined by comparing incongruent to congruent conditions (Inc > Con) across both groups. Second, the age-related effects on the executive control network were assessed by comparing the attentional conflict between the two groups (e.g., [Older (Inc > Con) > Young (Inc > Con)]).

Finally, univariate linear regression analyses were performed in the older group to identify how activations of brain areas within the executive control network (contrast Inc > Con) varied as a function of the flanker RT cost. Similar univariate linear regression analyses were also performed to link these activations with major demographic factors including education duration, history of falls (self-reports for past 12 months), as well as with clinical scores of interest as described earlier (cognitive, functional, and gait scores). The latter scores were entered as parametric covariates in our SPM analysis of the attentional conflict (activation for Inc > Con). Because gait variability is frequently related to gait speed, our regression analysis of gait variability was also performed with gait speed as a covariate of non-interest.

For all second-level whole-brain analyses, we report activations with significant p-values ($p < .05$) after family-wise error (FWE) correction for multiple comparisons across the whole brain. Activations surviving a statistical peak threshold of $p < .001$ uncorrected with a cluster size of >50 contiguous voxels, were also retained (Lieberman and Cunningham, 2009).

3. Results

3.1. Clinical scores and gait measures

Results from the cognitive, functional, and gait measures obtained in the order adult group are shown in Table 1. General cognitive assessment using MMSE and FAB indicated that our group of older participants performed within the normal range according to their age and education.

3.2. Behavioural data from the flanker task

Detailed AC and RT results obtained during the flanker task are presented in Supplementary Table 1 and Fig. 1. Overall participants were more accurate in the congruent (M = 99%; SD = 3) than incongruent condition (M = 95%; SD = 11; V = 342; $p < .001$). Regardless of conditions, older adults were less accurate (M = 95%; SD = 10) than young adults (M = 99%; SD = 1; W = 191; p = .02). Moreover, the flanker accuracy cost was larger in older (M = 6%; SD = 13) than younger participants (M = 1%; SD = 2; W = 440; p = .05).

The ANOVA on RT data revealed a significant main effect of condition ($F_{(1,102)} = 11.5$; p = .001), with faster answers in the congruent (M = 659 ms; SD = 137) than incongruent condition (M = 779 ms; SD = 189), and a main effect of age, with younger being faster (M = 591 ms; SD = 97) than older participants (M = 792 ms; SD = 168) ($F_{(1,102)} = 10.45$; p = .001). A non-parametric analysis on the flanker RT cost between groups also revealed a larger interference in the elderly than the younger (respectively M = 146 ms; SD = 106 and M = 74 ms; SD = 35, W = 521; p = .001).

Finally, of note, for older participants, the flanker RT cost showed a positive correlation (Spearman Rank, $r_s = 0.36$; $p < .03$) with the stride

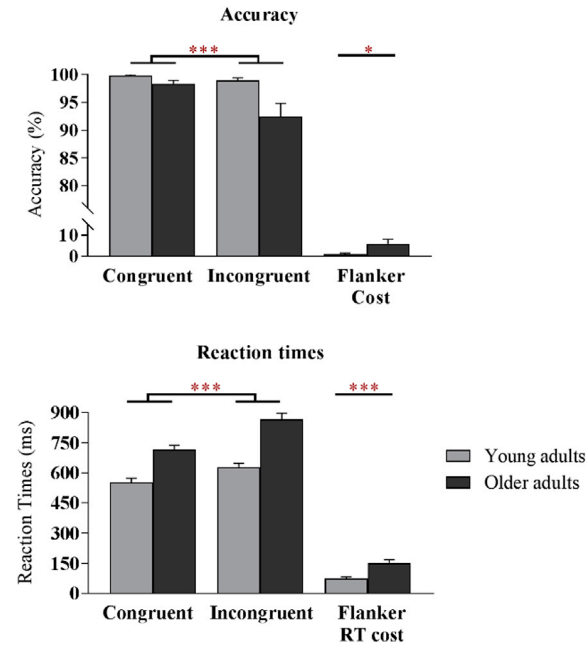

Fig. 1. Behavioural results from the Eriksen flanker task for young and old adults separately. **Upper panel**: Mean accuracy (%) for congruent and incongruent trials, as well as the flanker accuracy cost. **Lower panel**: Mean reaction times (in milliseconds) for congruent and incongruent trials, as well as the magnitude of the flanker RT cost. All graphs are depicted with bars for standard errors of the mean (SEM) and p-values (asterisks) with the following significance level: * $p < .05$; ** $p < .01$; *** $p < .001$.

length CV under the simple walking condition. The flanker RT cost did not show any other significant correlation with other gait parameters or with cognitive and functional scores. The RT cost did not correlate with age either (p = .09).

3.3. fMRI data

3.3.1. Influence of age on the executive control network

A main effect of executive control (incongruent > congruent flanker trials) across the two groups ($p < .05$ FWE) was found in a widespread brain network that encompassed several prefrontal areas, including bilateral frontal eye field (FEF), inferior frontal gyrus (IFG), left superior frontal gyrus (SFG), and dorsal anterior cingulate gyrus/supplementary motor area (dACC/SMA). In addition, there were prominent temporo-parietal activations including bilateral increases in the superior parietal gyrus (SPG) and intraparietal sulcus (IPS), plus right-lateralized peaks in the inferior temporal cortex (ITG). Bilateral activations were also found in the inferior and medial occipital gyri (IOG and MOG, respectively) as well as in the posterior cerebellum (Table 2A and Fig. 2).

A direct between-group comparison revealed higher activation for the elderly during executive control ($p < .001$ uncorrected and cluster size > 50 voxels) in the posterior parietal cortex and dorsal parieto-occipital sulcus (POS), predominantly left-lateralized. This age-related difference was specifically associated with increased activation during incongruent trials, as shown by post-hoc unpaired *t*-test performed on beta values extracted from these clusters (Supplementary Figure 2).

3.3.2. Executive control network modulated according to clinical scores

Linear parametric regression analyses (Table 2B and Fig. 3) were performed to investigate how individual differences in cognitive performance, functional scores, and gait parameters were related to brain activity patterns in older adults. These regression analyses revealed that higher gait variability during normal walking condition (NW) correlated with higher activations of several cortical areas within the executive

Table 2
Localization (MNI coordinates) and peak activation values (z score) for brain areas engaged during executive control. (**A**) Main effects of conflict and interaction with age group (Inc > Con x Old > Young), and (B) parametric increases related to clinical scores and gait parameters in the elderly. In (**A**), shared activations across both groups are listed in the upper part of the table, while activations greater in the older than the younger group (between-group analysis) are listed in the bottom part. In (**B**), the reported stride length CV and stride time CV were measured under normal walking conditions. All reported peaks are significant at $p < .001$ uncorrected for multiple comparisons with cluster extent > 50 voxels. Abbreviation: Con: Congruent condition. Inc: Incongruent condition. Lat.: Hemisphere lateralisation. NW: Normal walking. CV: Coefficient of variation. Z-score values refer to the activation maxima to the SPM coordinates.

Region		Lat.	Z score	MNI Coordinates		
				x	y	z
(A) Executive control (Inc > Con)						
Common activations across both groups						
Frontal	Superior gyrus	R	3.63	24	8	58
	Superior gyrus	L	5.55	−24	−4	52
	Frontal Eye Field	R	5.31	45	11	28
	Frontal Eye Field	L	4.55	−39	5	37
	Inferior gyrus	R	4.78	54	32	28
	Inferior gyrus	L	4.15	−51	8	40
	Posterior-Medial – dACC/SMA	R	4.17	3	20	52
	Posterior-Medial – dACC/SMA	L	4.16	−3	23	49
Parietal	Superior posterior gyrus	R	6.56	27	−73	58
	Superior posterior gyrus	L	5.93	−24	−67	49
	Intraparietal sulcus	R	6.03	39	−43	49
Temporal	Inferior gyrus	R	7.41	45	−70	−11
Occipital	Middle gyrus	R	6.80	36	−85	7
	Middle gyrus	L	5.42	−36	−91	7
	Inferior gyrus	R	6.38	36	−88	−2
	Inferior gyrus	L	6.33	−48	−76	−5
Other	Cerebellum – 7b (Uvula)	R	4.07	12	−49	−29
	Cerebellum – Crus 1	R	4.60	9	−76	−26
	Cerebellum – Crus 1	L	3.98	−9	−73	−23
Older > Young adults						
Parietal	Superior gyrus – Precuneus	L	3.77	−12	−79	49
Occipital	Dorsal parieto-occipital sulcus	L	3.37	−24	−85	37
(B) Executive control (Inc > Con) - Positively correlated with clinical scores						
Gait Parameters (NW)						
Stride length CV						
Frontal	Middle gyrus	R	4.04	30	11	55
Parietal	Superior gyrus - Precuneus	L	3.44	−6	−79	46
Occipital	Dorsal parieto-occipital sulcus	L	3.84	−24	−79	37
Stride time CV						
Occipital	Dorsal parieto-occipital sulcus	R	4.71	18	−88	40
Cognitive assessment						
Digit Symbol-Coding test						
Other	Cerebellum – Crus 1	R	3.99	33	−55	−38

control network ($p < .001$ uncorrected, cluster size > 50 voxels). Specifically, older adults showing high scores in stride length CV over-recruited both the right prefrontal cortex (MFG) and the left posterior parieto-occipital cortex (precuneus and POS) on incongruent trials, whereas those with high scores in stride time CV recruited more the right posterior parieto-occipital cortex. Similar peaks were found when the same whole-brain regressions of stride length and stride time were performed with gait speed taken as a covariate (since these parameters are frequently related), except for the left precuneus that did not pass our threshold of $p < .001$. Neither regression analyses with gait speed alone revealed any significant effect, nor those using gait characteristics under the dual-task walking conditions (i.e., SDW and CDW). Similar regression analyses with functional assessment scores (i.e., TT, TUG and SPPB) showed no significant effect. In contrast, regression analysis with scores from cognitive tests revealed a selective correlation between greater activity in the anterior cerebellum and better performance on the DSC test. There was no effect however within the executive control networks. No association was found for the other cognitive tests (i.e., FAB and MMSE).

Finally, regression analyses using the flanker RT cost from each individual subject and demographic information (i.e., age, education, history of falls) as parametric covariate revealed no quantitative relationship with brain activations during the executive control (Inc > Con) in the older group.

4. Discussion

In the present study, we determined the influence of age in brain activity associated with executive control and examined their relationship with alterations in cognitive function and gait parameters that are major predictors of fall risks in the elderly. To this aim, we obtained fMRI data during a flanker task allowing us to probe for both selective processing and response conflict resolution components of attention. Our results showed that gait impairment, specifically spatio-temporal variability measures, was associated with greater recruitment of frontal and parietal areas during a flanker task, while other functional and cognitive tests did not exhibit such relationship.

Consistent with prior studies, we demonstrated that all participants were sensitive to distracting visual stimuli, as indicated by longer reaction times and more frequent errors on incongruent than congruent trials in the flanker task (Botvinick et al., 1999; Casey et al., 2000). Although the elderly still achieved good results overall, they were globally less accurate and slower than younger adults. Importantly, however, incongruent flankers led to consistently larger performance costs in the elderly relative to the younger group which may reflect an attenuation of inhibitory control processes (Hasher et al., 2007; Zhu et al., 2010).

Also in agreement with previous work, a distributed fronto-parietal-occipital network was recruited during the flanker task, overlapping with areas implicated in executive control across various paradigms (Casey et al., 2000; Fan et al., 2005), thus demonstrating globally similar cognitive control mechanisms engaged regardless of age (Langenecker et al., 2004; Zhu et al., 2010). Activation patterns predominantly involved bilateral areas in the superior lateral prefrontal cortex (SFG) and more medial areas in dACC/SMA, respectively associated with response selection (Casey et al., 2000) and conflict monitoring (Botvinick et al., 1999). Bilateral activations were also found in the FEF, SPL, and IPS, a network typically linked to top-down mechanisms controlling selective attentional components of executive control (Corbetta and Shulman, 2002; Collette et al., 2006), together with increases in occipital visual areas (IOG and MOG), presumably reflecting enhanced target processing (Hopfinger et al., 2000; Zysset et al., 2007; Korsch et al., 2013).

Despite the substantial overlap of activations, a direct between-group comparison revealed greater activation in the left posterior parieto-occipital cortex (encompassing precuneus and POS) in older compared to younger adults, reflecting greater demands to process the central target during incongruent trials. Notably, the precuneus is consistently activated by voluntary shifts of attention during task switching (Piguet et al., 2013) to guide attentional resources to relevant information (Shulman et al., 2009), and bilateral parietal activations (including precuneus) appear more common in older adults (Nielson et al., 2002; Zhu et al., 2010), while similar tasks elicit only unilateral activity in young adults (Huang et al., 2012). Although bilateral fronto-parietal recruitments have been interpreted as age-related compensatory strategies (Cabeza, 2002; Davis et al., 2008), frequently reported in neurocognitive aging studies (Cabeza, 2002; Colcombe et al., 2005) or in seniors with high risk of falling (Colcombe et al., 2004), the activity enhancement observed in our elderly might not be sufficient to fully mitigate a relative decline in executive

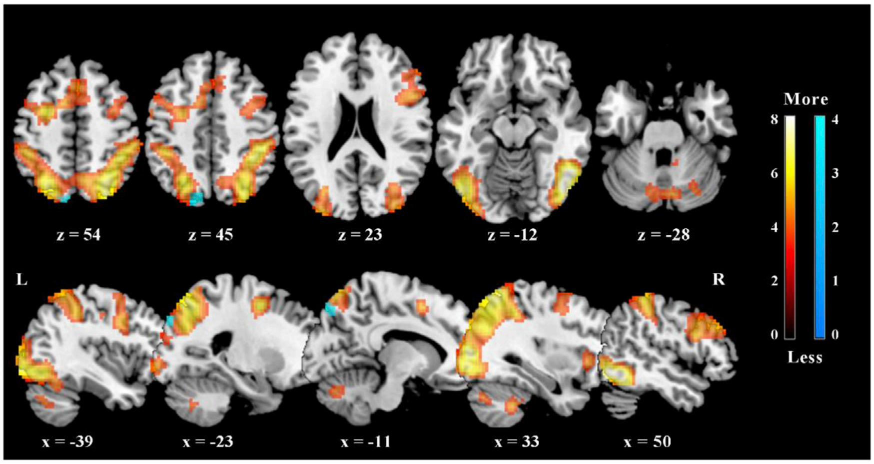

Fig. 2. Brain activations evoked by executive control during conflict trials (Inc > Con) in the flanker task. **The areas** were commonly recruited across both age groups pooled together. Brain activation related to conflict trials is presented as of the degree of brain activation. Greater increases were observed in the older adults (compared to young adults) for posterior parietal areas, depicted in blue (group × conflict interaction). All clusters are significant at the peak-level at p < .001, uncorrected for multiple comparisons, with a minimum size of 50 voxels.

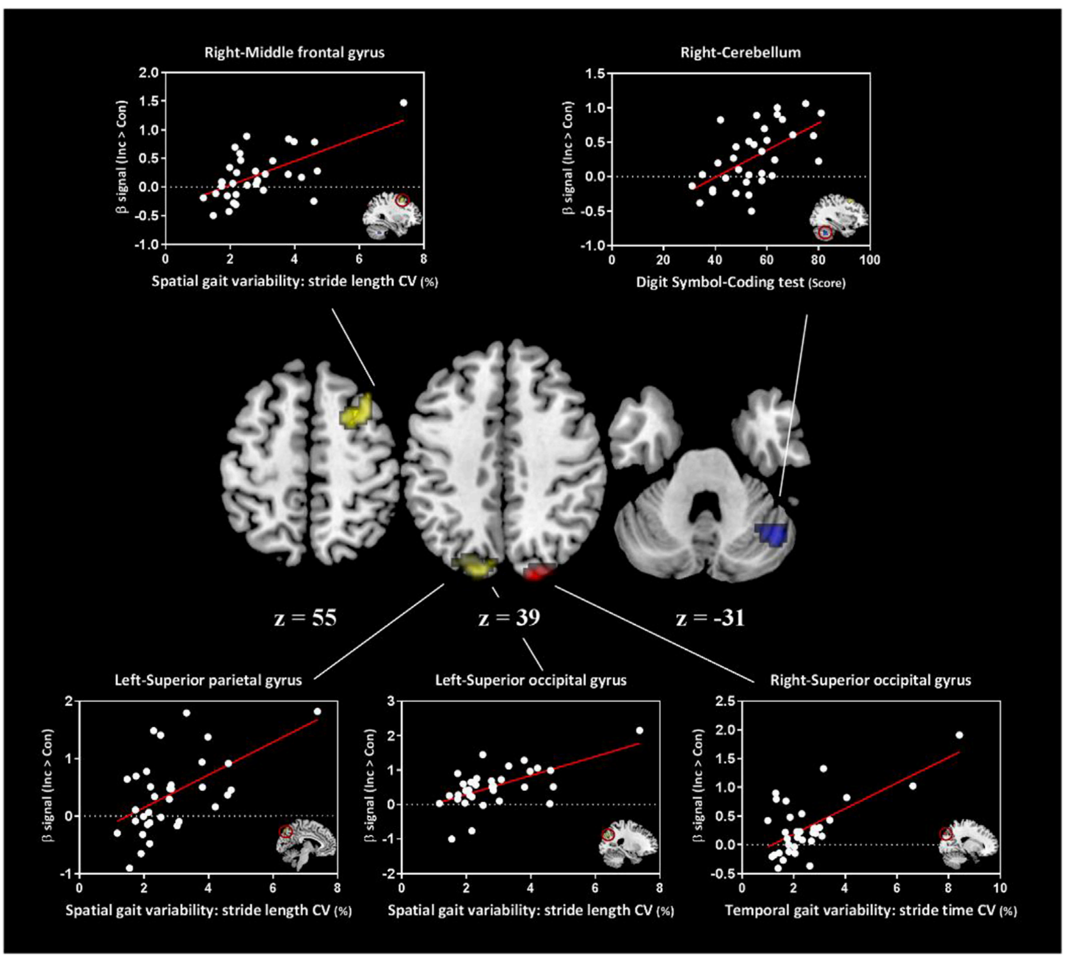

Fig. 3. Illustration of the cerebral areas engaged by executive control (contrast Inc > Con) and whose activity exhibited a positive correlation with clinical scores in whole-brain SPM analysis. Activations associated with an increase in the temporal variability of gait (stride time CV) are shown **in red**, those associated with spatial variability of gait (stride length CV) **in yellow**, and those associated with better cognitive performance (Digit Symbol-Coding test) **in blue**. Individual scores and activation parameters (betas) from these clusters are plotted to illustrate these correlations and remained significant when considering all participants or when removing outlier participants (rs > 0.42 in all cases), except for the right-superior occipital gyrus (p > .05). All SPM clusters are significant at the peak-level at p < .001, uncorrected for multiple comparisons, with a minimum size of 50 voxels.

control. The age-related increases in posterior parietal areas may rather suggest a limited capacity to optimally recruit brain systems mediating executive control under challenging situations, as reflected by the mild but consistent decrease in behavioural performance (i.e., lower AC and longer RT) observed in the elderly.

Critically, we investigated how these brain activity patterns engaged by executive control in the elderly related to their gait performance and to cognitive and functional tests predicting fall risks. While behaviourally we found a significant correlation between the flanker interference magnitude (RT cost) and spatial gait variability, our fMRI results revealed that elderly with more variable gait tended to over-recruit both the right MFG and left posterior parieto-occipital areas (SPL and POS) during attentional conflict. Strikingly, these posterior activations overlapped exactly with regions showing age-related increases during distraction by incongruent flankers (see Figs. 2 and 3). As gait variability is a major predictor for fall risks (Hausdorff, 2005), our results provide novel support to suggest that gait irregularity in the elderly is associated with specific decrements in executive control (Sheridan and Hausdorff, 2007), and to link this common decline to both frontal and posterior parieto-occipital areas in the brain. These data aligned well with other recent findings suggesting that gait variability is associated with differential activity and connectivity of posterior cortical areas in the superior parietal lobule (SPL) (Bürki et al., 2017; Lo et al., 2017). Moreover, higher SPL activation during an attention-demanding task was also reported in elderly individuals with poorer executive control performance and higher variability in lower-limb movements (Bürki et al., 2017). In line with these results, locomotion alterations have been linked to the integrity of connections between cerebral areas associated with executive control (Jor'dan et al., 2017; Lo et al., 2017). In particular, in a recent paper, Lo and colleague reported that the degree of anti-phase functional connectivity between the default mode network and the superior parietal sulcus (encompassed in the dorsal attention network) was correlated with an increase of age-related gait variability, while gait velocity was associated with stronger connectivity of MFG with the fronto-parietal executive network. Overall these results dovetail with our findings, demonstrating the importance of both the SPL/precuneus and MFG in age-specific changes in executive control and their implication in gait pattern deficits. By playing a key role in integrating endogenous task goals with external sensory cues (Piguet et al., 2013), these posterior parietal areas may contribute to the swift coordination of motor behaviour and executive control processes during steady walking, and thus be over-recruited in older adults with gait difficulties.

We note a predominant left-lateralized increases in parieto-occipital areas that showed age-related effects and correlated with gait spatial irregularity in our elderly participants. This may at first appear at odds with previous work suggesting a specialisation of the right hemisphere in locomotion (Barbieri and Vitório, 2017). In particular, right-lateralized fronto-parietal areas implicated in the processing of stimulus-driven shifts of attention and the integration of lower-limb proprioceptive efferents have been associated with gait abilities (Lo et al., 2017) and body balance control in the healthy elderly (Goble et al., 2011), as well as in individuals with hemispheric strokes (Duclos et al., 2015). A plausible explanation for the current laterality effects may be that elderly with gait disturbances fail to engage specialized cortical processes (i.e., in the right hemisphere), but instead recruit a more widespread and more bilateral network of brain areas (i.e., with an additional recruitment of the opposite left hemisphere), which wold accord with similar findings in other tasks and attributed to age-related losses in brain functional specificity (i.e., dedifferentiation) (Dustman, 1985; Park et al., 2004).

While we found a correlation with increased activity in right MFG and gait variability (stride length), we found no main effect of age distinguishing older from younger individuals in prefrontal areas. However, functional reduction in SFG and medial prefrontal areas have previously been observed for fallers (Nagamatsu et al., 2013) during executive control task, while a reduction in the dorsolateral prefrontal cortex (DLPFC) and SMA were observe in elderly individuals with high gait variability (Shimada et al., 2013). Receiving inputs from multiple sensor cortices, the DLPFC is an area crucially implicated in both conflict resolution (Casey et al., 2000) and divided-attention (Johnson et al., 2007; Yildiz and Beste, 2015). While the relationship between right MFG and gait variability is broadly consistent with these previous findings, the lack of a main age-related effect might be explained by the fact that our flanker task was designed only to recruit and probe for executive control network, but not challenging enough to induce a differential recruitment of prefrontal areas. Furthermore, although DLPFC vulnerability to ageing is well established, several neuroimaging studies reported inconsistent findings, including no difference in DLPFC activations between age group (Liu-Ambrose et al., 2008), over-recruitment in the elderly as a function of task difficulty (Chen et al., 2017; Mirelman et al., 2017) or age-related deactivation when cognitive load becomes too important (Reuter-Lorenz and Cappell, 2008). Taken together, these findings highlight how prefrontal effects may depend on particular task characteristics. In addition, we did not find an increase of DLPFC recruitment as a function of behavioural performance (Casey et al., 2000; Nielson et al., 2002; Huang et al., 2012) in the flanker task or in other neuropsychological tests. Nevertheless, we did find that older adults with poor cognitive processing speed (digit symbol coding task) exhibited lower activity in the right cerebellum, a structure that is densely connected to pre-frontal areas and whose information processing functions can mimic those intrinsic to frontal cortices (i.e., cerebellar cortical forward model) (Ramnani, 2006). Moreover, cerebellar activity has been reported to mediate conflict resolution (Konishi et al. 2005; Schweizer et al., 2007) and to be altered in individuals with higher fall risks (Liu-Ambrose et al., 2008). Together, these data therefore support the view that functional changes in the cerebellum may contribute to both cognitive and motor dysfunction in the elderly.

Notably, the current study did not reveal any association of brain activation patterns with gait characteristic measured under dual-task walking conditions or with functional tests, such as the TUG. This contrasts with previous reports that the latter test may predict poor executive functioning in the elderly (McGough et al., 2011) and that changes in the gait pattern under dual-task conditions are associated with cognitive deficits (Bridenbaugh and Kressig, 2015). Therefore, our findings suggest that locomotion control under single-task (i.e., normal walking) and dual-task conditions might be associated to partly distinct components of cognitive control and their corresponding cerebral substrates. While gait abilities under normal walking might rely on intact mechanisms of selective attention and control of endogenous task goals mediated by posterior parietal areas, as demonstrated here, gait abilities under dual-task conditions as well as complex motor sequences (measured by functional tests such as the TUG) might rather be more dependent on other cognitive processes such as divided attention and working memory components (Collette and Van der Linden, 2002; Collette et al., 2005). This hypothesis should be investigated in further studies, e.g., by directly assessing the neural interplay between gait alterations under dual-task walking conditions and multitasking abilities in elderly individuals and their link with fall risks.

In sum, the present study highlighted that among geriatric tests frequently used in clinical routine to probe gait difficulties due to relative declines in cognitive performance, the assessment of spatio-temporal gait variability (such as stride length and stride time) using electronic devices (such as GAITrite) might provide a particularly sensitive and objective tool to identify neural changes in executive control networks in the elderly and better estimate prospective fall risks in these individuals.

We acknowledge several potential limitations in our study. First, statistical adjustments used to test some correlations between cerebral activity and clinical assessments scores are relatively arbitrary. In particular, the Bonferroni correction, applied in our study to counteract problems with multiple comparisons, is considered as a relatively conservative procedure and might therefore have increased the number of true negative results. Another limitation is that our population sample recruited only elderly with high fall risks based on clinical criteria, allowing us to focus our analyses on cognitive, gait, and neural markers that are specifically present in these at-risks individuals. Although falls may also occur in the absence of cognitive or motor disorder, they are likely to reflect a particular frailty in some individuals, and our recruitment ensured to select at risk participants. Further studies might fruitfully include a control group exhibiting no risk of falls, to assess whether the functional changes observed here are also present in elderly with more optimal aging profiles, or determine potential neural markers for such resilience. Concerning the calculation of the gait variability, we also recognize that capturing a greater number of passes per gait condition may further have improved the stability of the measurements. Finally, due to unexpected gender differences in the recruitment of older volunteers, we selected only female participants. Although there is no reason to believe that our findings would interact with gender differences, it will be important to extend and confirm our results with elderly male participants.

5. Conclusion

The present study sheds new light on the neuroanatomical substrates of executive control processes modulated by aging, and their relation to gait difficulties that are predictors of falls. While both young and older adults recruited a similar fronto-parieto-occipital network during attentional conflict conditions, we found age-specific over-recruitment of the precuneus and dorsal parieto-occipital cortices that might reflect compensatory processes mitigating executive control dysfunction due to aging. Critically, high gait variability in our elderly was predicted by both larger attentional interference and greater increases in both frontal and parieto-occipital areas in response to incongruent flankers. In addition, the right cerebellum was less activated in the elderly with poorer processing speed scores. Our study provides novel evidence for a close relationship between gait impairment and executive control abilities, and highlights specific brain areas (in parietal cortex and cerebellum) as potential regions of interest for future research on fall risks.

Funding

This work was funded by grants from Geneva University Hospitals (HUG), the Panacée Foundation, the Jaques-Dalcroze Institute (IJD), the National Center of Competence in Research (NCCR) Affective Sciences, the Swiss National Science Foundation (SNSF), and an award of the Geneva Academic Society (Foremane Fund), Switzerland.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2019.01.030.

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