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Gait and Cognition: A Complementary Approach to Understanding Brain Function and the Risk of Falling

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Abstract

Until recently, clinicians and researchers have performed gait assessments and cognitive assessments separately when evaluating older adults. Increasing evidence from clinical practice, epidemiological studies, and clinical trials shows that gait and cognition are inter-related in older adults. Quantifiable alterations in gait among older adults are associated with falls, dementia, and disability. At the same time, emerging evidence indicates that early disturbances in cognitive processes such as attention, executive function, and working memory are associated with slower gait and gait instability during single and dual-task testing, and that these cognitive disturbances assist in the prediction of future mobility loss, falls, and progression to dementia.

This paper reviews the importance of the gait-cognition inter-relationship in aging and presents evidence that gait assessments can provide a window into the understanding of cognitive function and dysfunctions, and fall risk in older people in clinical practice. To this end, the benefits of dual-task gait assessments (e.g., walking while performing an attention-demanding task) as a marker of fall risk are summarized. Further, we also present a potential complementary approach for

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Conflict of Interest

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reducing the risk of falls by improving certain aspects of cognition through both non-pharmacological and pharmacological treatments.

Untangling the relationship between early gait disturbances and early cognitive changes may be helpful for identifying older adults at higher risk of experiencing mobility decline, falls and the progression to dementia.

Keywords

Falls; Mild Cognitive Impairment; Dual-task; Cognitive function; Gait Variability

Cognitive Impairment and Falls: A Well-Known Couple

An important goal of geriatric medicine is to reduce the gap between overall life expectancy and disability-free life expectancy. Two major geriatric problems contribute to this gap: cognitive impairment and gait impairment. Frequently, these impairments can lead to disabling forms of dementia as well as falls. Importantly, dementia and falls often co-exist in older adults; gait impairments and falls are more prevalent in patients with dementia than in normal aging and are related to the severity of cognitive impairment.[1] Additionally, gait and cognitive impairment are prominent independent risk factors for falls. Falls are a common geriatric syndrome affecting about a third of older adults each year, and dementia has a prevalence of 8% in older adults aged 65 and older, and 35% in people over age 85. A better understanding of the relationship between cognitive impairments and gait impairments may help clinicians and researchers to develop interventions and institute preventive measures to delay the transition to falls and dementia and promote disability-free life expectancy.

Falls are a major cause of morbidity among older adults, especially for those with cognitive problems. For instance, older adults with moderate to severe cognitive impairment have a higher risk of falls, with an annual incidence of around 60–80%; twice the rate in cognitively normal older adults.[2] The consequences of falls in the population of demented older adults are very serious; fallers with cognitive problems are approximately five times more likely to be admitted to institutional care than people with cognitive issues who do not fall.[3] They are also at high risk of major fall-related injuries such as fractures and head injuries that increase mortality risk. In addition to indirect costs and caregiver burden, the direct costs of emergency, acute, rehabilitation and long-term care are substantial and increasingly unsustainable for the healthcare system.

The precise mechanisms underlying the increased fall risk in cognitively impaired older adults are not completely understood. It has been shown that impaired cognitive abilities can reduce attentional resource allocation, which can compromise postural and gait stability.[4] Executive function is an essential cognitive resource required for normal walking; impairments in this cognitive domain are associated with both dementia and fall risk.[5] One specific early change in gait seen among older adults with mild to moderate dementia is a decrease in gait velocity.[1] The inter-relationship between cognitive deficits and gait disturbances has been attributed to specific brain networks such as the prefronto-parietal and cingulate areas that are selectively affected by diseases that accompany, but are not necessarily caused by, aging.[6]

The inter-relationship between cognitive and gait dysfunction has also been found in otherwise healthy older adults who have subtle cognitive deficits that are not yet profound enough to be identified using global measures of cognitive status. Such findings challenge our understanding and the definition of what is currently considered clinically relevant cognitive impairment. For instance, even among healthy older adults with “normal”

cognition as assessed using cutoff scores on global clinical measures of mental status, such as the Mini Mental Status Exam, low performance in executive function was prospectively associated with falls.[7]

A systematic review and meta-analysis of 27 prospective cohort studies with at least one year of follow-up among healthy community-dwelling older adults found that executive dysfunction, a subtle cognitive deficit, was associated with an increased risk for any fall [Odds Ratio: 1.44, 95%CI (1.20–1.73)] and falls associated with serious injury.[8] Similarly, early mobility decline, assessed as slowing of gait, has been found to co-exist or even precede the onset of clinically demonstrable cognitive decline in older adults.[9] This slowing of gait may have its onset up to 12 years before the clinical presentation of cognitive changes in older adults who later convert to mild cognitive impairment syndrome (MCI). This intriguing and provocative time course suggests that we may be able to augment the prediction of cognitive decline based on a simple and objective gait evaluation in the future. However, further work is needed before this idea can be applied to clinical practice.

MCI is seen as a transitional state between normal aging and early dementia. The prevalence of MCI can reach as high as 19% among older adults and increases to 29% in those over age 85.[10] People with MCI have a 10 to 15 times higher risk of developing Alzheimer's disease (AD), as well as a higher risk of falling compared with age-matched controls.[11;12] Recent studies have also shown that older adults with MCI have a higher prevalence of gait impairments compared to cognitively normal older adults.[12–14] Thus, older adults with MCI can be seen as a population at risk, not only for future dementia, but also for falls, and should perhaps be specifically targeted for interventions to reduce these dual risks.

Until recently, falls and dementia were studied and assessed as distinct geriatric syndromes (see Figure 1a). This may have led to a gap in our understanding of the cognitive-motor interactions that affects the pathways to disability in older adults. This gap may also explain why cognition has received little attention with regard to intervention strategies for falls prevention. As we detail below, we suggest that the time has come to view these two geriatric syndromes as interrelated outcomes associated with aging (see Figure 1b).

Cognition and gait instability

Although walking has long been considered a primarily automatic motor task, emerging evidence suggests that this view is overly simplistic.[15] Walking in the real world requires paying attention to various environmental features and recovering from postural perturbations to avoid stumbles or falls. Therefore, it is not surprising that deficits in attention and executive function processes are independently associated with risk of postural instability, impairment in activities of daily living, and future falls.[5]

The dual-task paradigm and risk of falls

The seminal "stops walking while talking" study by Lundin-Olsson et al.[16] showed that the inability to maintain a conversation while walking is a marker of future falls in older nursing home residents. Observing people walking while they perform a secondary attention-demanding task, the "dual-task paradigm", has been used to assess the interactions between cognition, gait, and the risk of falls. During the dual-task, the subject performs an attention-demanding task while walking to assess any modifications, compared to the reference, single task condition, in either the cognitive or the walking subtasks.[4] The underlying hypothesis is that two simultaneously performed tasks interfere and compete for brain cortical resources.[5] Gait modifications (also known as dual-task costs), such as slowing of gait, are interpreted as the increased cost of involvement of cortical attention processes while walking. The role of dual-task costs as a marker of future falls has been evaluated with

mixed results in the literature, perhaps, due to the heterogeneity of studies, small sample sizes, limited prospective fall ascertainment, and the lack of standardization in dual-task procedures. Despite these limitations, a recent systematic review suggested that an increased dual-task cost during gait assessment is associated with an increased fall risk in older adults.[17] A study among 1,038 older adults found that a dual-task cost of 18 % or more prospectively predicts falls in individuals who walk at 95 cm/s or faster [Odds Ratio: 1.07, 95% CI (1.04–1.10)], highlighting the sensitivity and predictive ability in older adults who have a relatively intact gait.[18] Although clinically meaningful cut off values of dual-task costs are still controversial and other unanswered questions remain, a growing body of evidence supports the potential clinical utility of this paradigm for falls prediction: it is neither costly nor invasive, can easily be implemented, and provides a valid and sensitive means of assessing motor-cognitive interactions and fall risk.

The dual-task cost identified during a gait assessment may reveal subtle brain impairment[14] and have been related to attention and executive function efficiency.[19;20] For example, patients with AD and patients with Parkinson's disease who have greater deficits in executive function than age-matched controls show a larger dual-task cost when compared with cognitively normal older adults who experienced a much less pronounced dual-task cost.[19] In this way, the dual-task assessment may represent impaired brain capacity to share cognitive resources between walking and an attentionally demanding task, placing the subject at an elevated fall risk while performing these concurrent tasks.

Gait variability and risk of falls

Gait is a complex motor behavior with many measurable facets. This growing field of research provides an interesting window for the study of the regulation of the locomotor and cognitive control. Gait velocity is easily measured and provides valuable information about physical and medical status in the complete functional spectrum of older people.[21;22] Another way to quantify gait instability that has garnered much attention in the literature recently is gait variability.

Changes in gait velocity and variability are not mutually exclusive; however, they provide different information. For example, Herman et al. reported that gait variability during dual-tasking predicted future falls among community-living older adults during 2 years of follow-up, while gait velocity did not.[7] The variability of several spatio-temporal gait parameters has been studied, with stride to stride fluctuations in gait cycle timing (e.g., stride time) being the most widely reported. The reasons for the popularity of this measure have been discussed elsewhere.[23] In brief, it has been suggested that stride time reflects one of the final pathways of the outcomes regulated by the central nervous system. Stride time variability is becoming a relevant marker of gait stability, both in research and clinically, and can be measured easily and robustly.[23] The general assumption is that there is an inverse association between stride time variability and gait stability. Low stride time variability reflects automatic processes that require minimal higher cortical input and is associated with efficient and safe gait patterns.[23] Walking is one of the most repetitive and "hard wired" human movements; the normal fluctuations in stride time variability are usually below 3% among healthy adults.[23;24] However, higher gait variability has been described in older adults with frailty[25], Parkinson's disease[26] and in AD[19;27], and prospectively associated with a high risk of future falls and mobility decline.[28;29] More interestingly, high stride time gait variability has been shown to predict future falls in community-dwelling older adults, [7;30] even when gait velocity failed to demonstrate an association. Previous work has shown that gait variability not only serves as a clinically relevant approach in the evaluation of mobility, but may also be responsive to fall prevention interventions.[23;24]

Variability in stride time and stride length are related to the control of the rhythmic stepping mechanism and should, therefore, be considered as markers of adaptability to the walking environment. Sheridan et al. reported that high gait variability could be a sensitive marker of dysfunction in the frontal cortical control of walking in subjects with moderate A D and executive dysfunction.[19] Hausdorff et al. showed that the degree of executive function efficiency was correlated to the degree of stride time variability.[15] These and other studies have shown that there is interplay between gait variability, cognitive dysfunction, in particular executive function and attention, and the risk of falls.

Gait changes may reflect cognitive impairment

Deficits in cognitive function and mobility co-exist in older adults even in the early stages of aging. Older people with MCI may have impairments in either memory (amnestic) or non-memory (non-amnestic) domains[18] as well as impairments in fine and complex motor skills, equilibrium, and limb coordination. Quantitative testing has revealed gait dysfunction in subjects with both the amnestic and non-amnestic MCI subtypes compared to healthy controls.[13] Neurological gaits, such as hemiparetic, and frontal or Parkinsonian gaits were almost twice as common in amnestic MCI as in normal controls in this study. Additionally, subjects with MCI and gait abnormalities (defined as either having slow gait or a neurological gait) were more disabled than subjects with MCI without gait abnormalities.[13]

Another study that included amnestic and non-amnestic MCI participants found that low performance in three related cognitive domains (i.e., attention, executive function, and working memory) was associated with slowing of gait velocity specifically under dual-task conditions, suggesting that these specific cognitive domains are relevant for maintaining a normal gait pattern in the presence of a cognitive load.[14] Recently, it has been shown that increased variability of time-related gait parameters were significantly different under dual-task testing in older adults with MCI compared to age-matched normal controls, but less affected than in people with mild AD.[27] The same group compared the effect of dual-task of different complexity between cognitively normal controls and older adults with MCI.[31] A significant dual-task cognitive status interaction was found for gait variability, but not for gait velocity, further demonstrating that gait variability may be especially sensitive to dual-tasking and to the complexity of the task given. The effect of complex dual-tasking (serial sevens subtraction while walking) on gait variability can be seen in Figure 2; stride time variability is larger in a subject with MCI, compared to a control participant.[31] These findings suggest that cognitive control of gait performance is impaired in people with MCI and in the early clinical stages of dementia. Interestingly, these disturbances were not evident during the single-task test condition. This finding highlights the ability of tests that challenge brain function to reveal subtle or early gait problems. In summary, several studies have shown that gait is altered in people with early cognitive problems, most prominently under dual-task conditions. These findings may provide an explanation for the high risk of falls in people with MCI.[12;32]

Strategies to prevent falls and enhance mobility

Fall prevention trials in cognitively normal older adult populations have demonstrated, with varying degrees of success, that both multifactorial (e.g., review of medications, strength and balance training, visual and hearing correction and environmental modifications) and single interventions (e.g., resistance exercises or progressive balance training) can be effective in preventing falls. In contrast, intervention studies targeting fall prevention in people with cognitive problems have been inconsistent or have only had modest success.[33] Older adults with cognitive problems, while at high risk for falls, represent a group who may be less responsive to the interventions that are effective among subjects that are cognitively intact. As discussed above, we further suggest that even subtle cognitive deficits may

compound the risk of falls in older adults whose cognition has not deteriorated to the level of impairment required to diagnose MCI or dementia syndromes.

In a recent systematic review, Oliver et al.[33] concluded in that the benefits of single and multifactorial interventions for fall prevention do not translate successfully from cognitively normal older adults to those with dementia. Additionally, Hauer et al. found that the effect of training on motor performance or fall prevention in older people with cognitive impairment is limited and clearly understudied.[34] There are several potential explanations for the lack of benefit of fall prevention programs in the cognitively impaired population including different underlying mechanisms for falls in those with cognitive problems and failure to address cognitive deficits adequately. Although much is known about the multifactorial nature of falls in cognitively normal individuals, our knowledge about the nature and inter-relationship of risk factors in those with cognitive problems is limited and, as a consequence, the number of falls and fall related injuries in this population continues to be problematic.

Therefore, the following questions are avenues for future inquiry: Is a new approach needed in fall prevention? Is the cognitive component missing in extant fall prevention interventions? Do we need to improve certain aspects of cognition, as a complementary intervention, in order to prevent falls in older adults? Is cognitive remediation needed in all older adults or only in the cognitively impaired? What age-associated changes in cognition should be defined as impairment?

Non-pharmacological approaches

Cognitive remediation interventions have been shown to improve attention and executive function as well as memory in older adults without dementia. Table 1 summarizes recent studies that have specifically evaluated the effects of interventions to improve cognition on gait and fall risk. Verghese et al.[35] conducted a pilot study in 24 older adults who were randomly assigned to either a computerized cognitive remediation intervention or a wait list. The ten participants who completed the cognitive remediation showed improvement on gait velocity during normal walking and walking while talking (dual-task) compared to baseline (Figure 3a). While the initial findings of this pilot trial need confirmation in larger scale trials, they indicate that a non-pharmacological cognitive intervention can positively modify gait performance, especially during dual-task testing.

Silsupadol et al.[36] conducted an intriguing but small study among 21 older adults with balance and gait impairment. Participants were randomly assigned to one of three interventions: single-task (active control), fixed-prioritization dual-task training and dual-task training with variable-prioritization. Improvements in balance and gait velocity were found in all groups after training (Figure 3b). However, when a cognitive, dual-task was added during testing, only participants who received dual-task training exhibited significant improvements in gait velocity ($p < 0.001$). Furthermore, the group that trained with variable-priority instructions demonstrated a dual-task training effect that was retained after 12 weeks of follow-up.[36] These results suggest that varying focus during training between the cognitive and motor tasks apparently had more benefits than training that required constant focus of attention on both tasks.

Schwenk et al.[37] conducted a randomized controlled trial (RCT) that evaluated the efficacy of a 12-week dual-task training program in 61 seniors with dementia. The intervention group received dual-task training, using progressively more complex activities such as walking while throwing and catching a ball or walking while performing mental arithmetic, during a two-hour exercise session carried out twice a week. The control group received low intensity exercise for one hour once per week over the same period of follow-up. After the 12 weeks

of training, the intervention group performed significantly better on gait in a complex dual-task condition ('walking while doing serial 3 subtractions') compared with the control group. Despite some limitations, including that the training in the intervention group included repeated exposures to the same dual-task test conditions that served as the main outcomes, this study shows RCT evidence[38] that dual-task training improve gait in people with mild to moderate dementia.

Finally, Mirelman et al.[39] reported an improvement in gait using a program of treadmill training enhanced with virtual reality in patients with Parkinson's disease. After six weeks of training, gait velocity, stride time and stride length significantly improved in usual and dual-tasking conditions as well as during over-ground obstacle negotiation (Figure 3c). In addition, gait variability decreased (i.e., improved) under dual-task conditions.[39] Moreover, the improvements in dual-task walking were much larger than that seen in a previous study that followed an almost identical treadmill training program, without the virtual reality component. This finding suggests that a complex motor-cognitive training may be more effective at improving dual-tasking and functional gait, compared to a program that focuses exclusively on motor function.

While the effects of these preliminary cognitive-based therapies to mediators of fall risk are promising, studies have not yet examined the impact of these interventions on fall frequency. Large scale RCT trials are needed to generate critical evidence-based results before this approach can be widely recommended.

Pharmacological approaches

Pharmacological interventions targeting attention and executive function have also improved gait performance in older adults.[40;41] Table 2 summarizes studies that specifically evaluate the effects of cognitive pharmacological interventions to improve gait and fall risk in older individuals. Methylphenidate (MPH) has been long used to improve attention in children with Attention Deficit Hyperactivity Disorder; however, its potential to modify motor function is less known. In a pilot study, Auriel et al.[40] evaluated the effect of a single dose (20 mg) of MPH on cognitive function, gait performance and markers of fall risk in 21 patients with Parkinson disease who were receiving L-dopa. A single dose of MPH was associated with a significant improvement in attention, executive function, gait velocity, stride time variability, and the Timed Up and Go Test, i.e., validated markers of abnormal gait and fall risk. Ben-Itzhak et al. tested the effect of MPH in 26 community-living older adults without dementia using a randomized, double blind, crossover design. MPH improved executive function, gait velocity and reduced gait variability in this sample of older adults as well.[41] Additionally, a single dose of MPH reduced the detrimental effect of dual-task testing on gait variability. These initial findings suggest that MPH, and potentially other drugs designed to enhance attention, may have a role as a therapeutic option for reducing fall risk in older adults.

Cognitive function and the brain control of gait also share several neurotransmitters that may serve as additional potential targets for pharmacological interventions. Dopamine deficits have been associated with fall risk in patients with Parkinson's disease; levodopa typically improves many gait features in patients with this neurological disease. Interestingly, however, a recent study that assessed the role of dopamine neurotransmission in fall risk[42] demonstrated that dopaminergic denervation is apparently not associated with falls in older adults with Parkinson's disease. Similarly, the neurotransmitter acetylcholine has shown to have an important role in cognitive function and in controlling gait and balance.[43] Specific regions within the brain with cholinergic tracts include the hippocampus, nucleus basalis of Meynert, basal ganglia, thalamus, and the pedunculopontine nucleus. The thalamic AChE

activity, which derives mainly from terminals of brainstem pedunculopontine nucleus neurons, plays a central role in the generation of the movement and gait and balance control.[44] The cholinergic system is also an important and specific controller of selective attention, likely an important factor in the dual-task decrement in walking that occurs in cognitively impaired adults. Therefore, correcting the cholinergic loss in dementia may improve attention and subsequently gait performance.

Cholinesterase inhibitors (ChEI), e.g., donepezil, galantamine and rivastigimine, are the currently approved symptomatic treatments for AD and vascular dementia. The molecular mechanism of action for ChEI is achieved by increasing cortical and hippocampal acetylcholine, regulators of memory and synaptic plasticity.[45] However, the mechanisms of clinical improvements in function in patients with dementia are not well understood. Possible explanations may relate to the cognitive action of the drug and to subtle improvements in motor function. For instance, there may be cognitive related and non-cognitive related enhancement mechanisms by which ChEIs might improve gait performance and potentially reduce fall risk.[43] Improving executive function and attention may affect gait control and cholinergic enhancement of the pedunculopontine nucleus may improve stride-to-stride variability. Both of these mechanisms have the theoretical potential to reduce the occurrence of falls. Whether by a direct effect or mediated through cognition, motor function improvement would consequently serve to stabilize mobility, reduce falls and delay functional decline.

A few studies have evaluated the effect of ChEI in motor performance in older adults. These are generally small scale, pilot investigations, but they are, nonetheless, worthy of consideration given their novelty and potential importance to our understanding of therapeutic possibilities. Two pilot studies evaluated the effect of ChEI on gait performance.[46;47] Assal et al. tested the effect of galantamine on gait in nine participants with moderate AD. Their gait was compared with 10 controls without dementia. Controls suffered a significant dual-task decrement in stride time, though there was no decrement among the participants with AD on galantamine. This finding suggests a galantamine-associated enhancement of the ability to adapt gait patterns to tasks that require attention. Montero-Odasso et al. assessed the effect of donepezil over four months of treatment on gait velocity and gait variability in six individuals with AD (see Figure 3d). Increases in gait velocity and a reduction in gait variability were seen at one month following treatment with the 5mg of donepezil. These benefits were further improved after four months of treatment when the full dose of 10 mg was achieved, suggesting a dose-response pattern. The control group, composed of eight individuals with MCI, experienced an expected reduction of gait velocity and an increase in gait variability over time. In a randomized crossover study involving 23 older participants with Parkinson's disease, Chung et al. observed that fall frequency was almost 50% lower when the patients were on donepezil than when they were taking a placebo.[48]

Memantine is another symptomatic treatment option for patients with moderate to severe AD. Recently, Beauchet et al. reported a memantine-related decrease in stride time variability among AD outpatients followed in a memory clinic, suggesting that decrease in gait variability may be explained by the combined dopaminergic and glutamatergic effects of memantine.[49]

These preliminary interventional studies provide a basis for testing a variety of approaches in larger clinical trials. If cognitive enhancers can change gait in a meaningful way, it could reduce the risk of falls, and in turn have a major impact on individual and societal outcomes. Currently, there are clinical trials under way to explore these interesting possibilities.[43]

Conclusions and Future directions

Falls are twice as common among people with cognitive problems and dementia, as compared with cognitively intact older adults. The classic multi-factorial fall risk intervention is not as effective in reducing fall risk in older adults with cognitive problems as it is in the cognitively normal adult. A potential explanation for this failure is that fall prevention strategies do not include “cognitive domains” as an intervention target.

New evidence and a fresh look at existing data on cognitive impairment, gait and mobility impairment and falls sets the stage for a novel approach and some practical conclusions. Cognitive impairment should be considered as a continuum from normal aging to advanced dementia, and, similarly, mobility decline and slowing of gait is a continuum that co-exists with or even precedes the declines in cognition. Cognitive impairment, gait decline, and falls, singly and together have a sufficiently high prevalence in older adults to constitute significant population health problems and important causes of disability. Gait variability is an objective measure that reflects cognitive dysfunction and may prove useful prognostically for mobility, cognitive and falls outcomes. Gait assessment under dual-tasking apparently can be used in the clinical encounter as a window into brain function in the early stages of the cognitive decline. Therefore, untangling the relationship between early gait and cognitive impairments may help identify older adults at higher risk of mobility decline, falls and progression to dementia.

Finally, improving certain aspects of cognition, specifically attention and executive function, in older adults can be a complementary way to treat mobility decline and risk of falls. In the cognitively impaired, this may be critical to reducing fall risk and its attendant disability. Exciting new preliminary studies have shown that both non-pharmacological and pharmacological interventions targeting cognition may improve gait performance, and consequently, have the potential to reduce fall risk. These interventions may be effective for improving mobility and reducing falls. It remains to be seen whether the pharmacologic and cognitive-training approaches would have a synergistic effect, whether one can substitute for the other, or whether one would eclipse the other. While important questions need to be addressed more fully, these initial investigations suggest that a complementary approach to fall prevention can be incorporated into the current fall intervention strategies.

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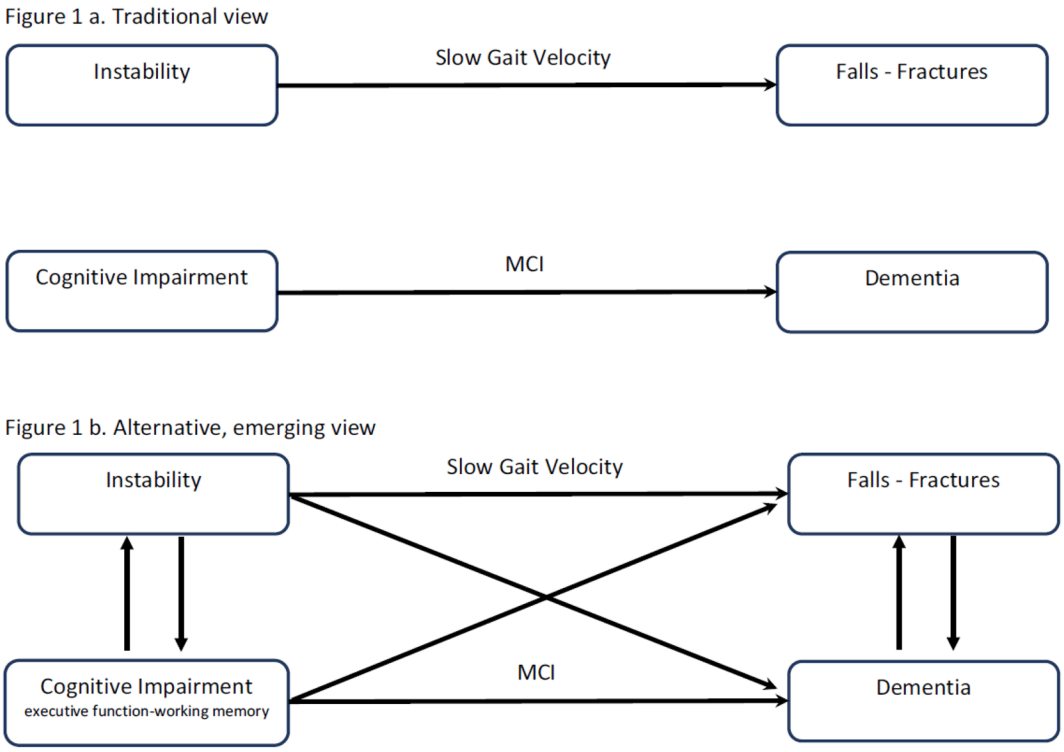

Figure 1.

Figure 1a and 1b. 1a Traditional view of the parallel decline of gait and cognitive function with aging. Gait performance and cognitive function deteriorate with aging yielding two geriatric entities: falls and dementia. **2b.** Alternative, emerging view. Cognition predicts mobility decline and falls, on the one hand; and, on the other hand, mobility decline and slow gait predict cognitive deterioration. These phenomena occur in a concurrent manner.

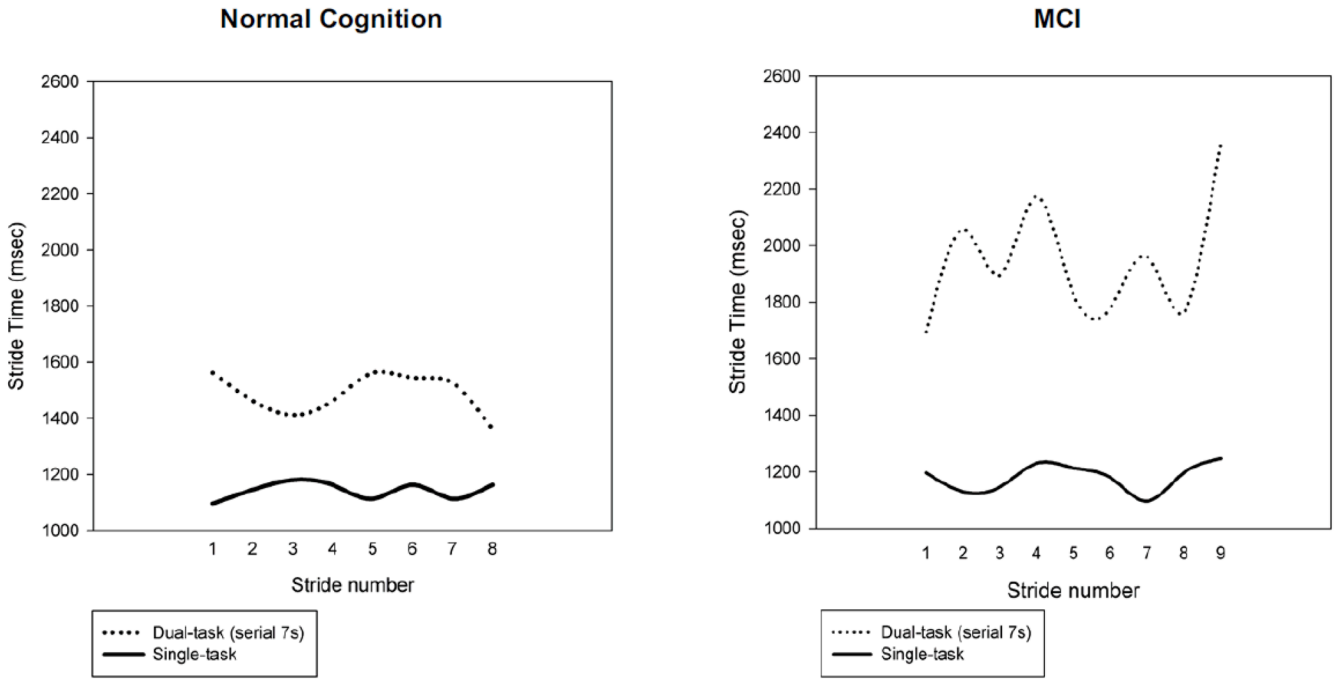

Figure 2.
Effects of a complex dual-task load (serials subtractions by sevens) on stride time variability in a participant with normal cognition (left) compared with a participant with mild cognitive impairment (right). From Montero-Odasso et al (2011)[31].

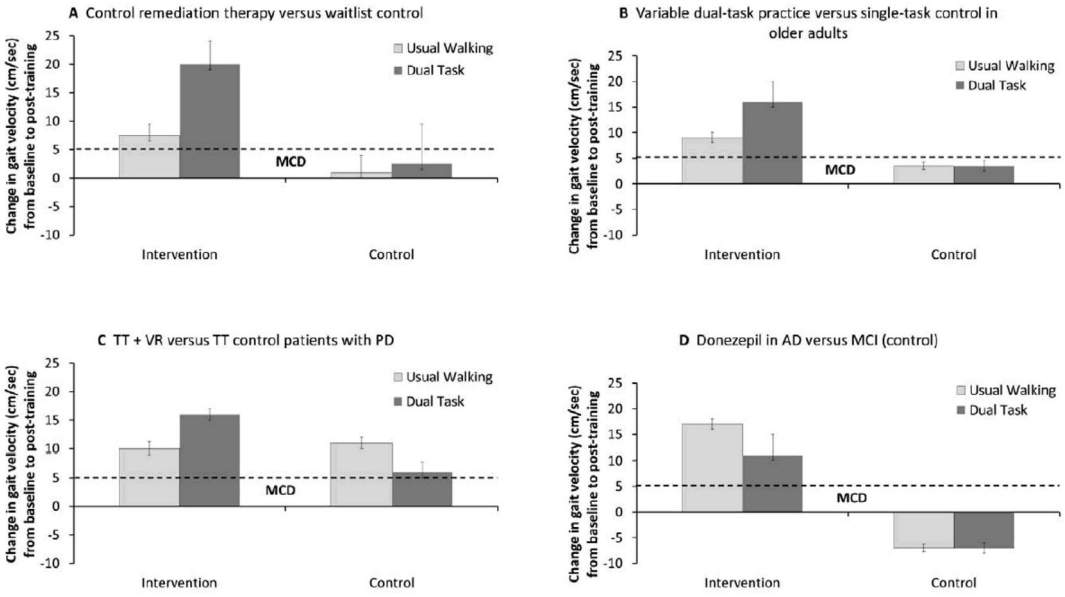

Figure 3.

Examples of the effects of four different forms of cognitive therapy on usual-walking gait velocity and dual-tasking gait velocity. Values shown are change with respect to baseline. Note: Note that 5 cm/s and 10 cm/s have been identified as the MCD and substantial difference (**3a)** Effects of 8 weeks of computerized cognitive training (while seated) in sedentary older adults, compared with wait list controls. Data from [35]. **(3b)** Effects of dual-task training during walking on gait speed in older adults with balance impairment, compared with subjects who only practiced walking. Data from [36]. **(3c)** Effects of 6 weeks of TT augmented with VR among patients with PD, compared with an active control comparison of 6 weeks of TT alone. Usual-walking gait speed increased in both the TT alone and TT + VR groups; however, DT gait speed only improved among the patients who participated in TT + VR. Data from [35;39]. **(3d)** Effects of 4 months of donepezil use on gait speed in patients with Alzheimer's disease and compared with control patients with mild cognitive impairment. Data from [47]. Adapted with permission from Segev-Jacubovski et al [50]. AD: Alzheimer's disease; DT: Dual-tasking; MCD: Minimal clinically significant difference; MCI: Mild cognitive impairment; PD: Parkinson's disease; TT: Treadmill training; VR: Virtual reality

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Table 1

Cognitive Training Interventions for Balance, Gait and Fall Risk

Study (year)	Study design	Type of intervention	Duration of training intervention	Participants	Summary of findings
You *et al.* (2009)	RCT	Dual-task CGI: simultaneous motor (walking 30 m) and cognitive (memory recall) task (n = 8), whereas the control group (n = 5) received a placebo treatment (walking while listening to simple music)	18 sessions, 30 min per session over 6 weeks	13 older adults (mean age: 68.3 ± 6.5 years) with a history of falls	Working memory performance under the dual-task condition improved ($p < 0.05$), but significant changes in gait velocity and stability were not observed
Silsupadol *et al.* (2009)	RCT	Participants were randomly assigned to one of three interventions: single- task training (n = 7), dual-task training with fixed-priority instructions (n = 8), and dual-task training with variable-priority instructions (n = 6)	12 sessions; 45-min individualized sessions, 3 times a week for 4 weeks	21 older adults (aged 65 years and older) with balance impairment	Improvement in balance and gait speed was found in all groups. Only the DT training with variable-priority instructions group demonstrated a DT training effect at the second week maintained at 12-week follow-up
Yogev-Seligmann *et al.*	Open-label, pilot	A 4-week program of one-on-one training included walking while performing several distinct cognitive tasks	12 sessions; three times a week for 4 weeks	Seven patients with PD (mean age: 63.8 ± 8.4 years)	Gait velocity and gait variability during DT significantly improved. Untrained DT also improved and was retained 1 month after the end of the training
Verghese *et al.* (2010)	RCT	Computerized 'Mindfit' program (n = 10). Each training session included a mixture of 21 visual, auditory and cross-modality tasks compared with wait-list (n = 10)	24 sessions; 45–60 min/session, 3 times a week for 8 weeks, compared with wait-list controls	Sedentary older adults (mean age: 77.4 ± 7.0 years, MMSE: 29 ± 0.3) at training, and wait-list (mean age: 79.9 ± 7.5 years; MMSE: 29.1 ± 0.4)	Gait velocity improved during normal walking ($p< 0.05$) and 'walking while talking' ($p = 0.002$) only in study group. Speed of processing improved significantly in the training group ($p = 0.03$)
Schwenk *et al.* (2010)	RCT	Intervention group (n = 20) underwent dual-task-based exercise training (motor: throwing or catching a ball and cognitive: arithmetic tasks, repeating names of animals). The control group (n = 29) performed low-intensity exercise.	24 sessions over 12 weeks, 1 h twice a week	49 participants (mean age: 81.9 ± 7.5 years) with confirmed mild-to-moderate dementia (MMSE 17–26: 21.4 ± 2.9)	DT training significantly improved gait velocity under dual-task ($p< 0.001$), cadence ($p = 0.007$), stride length ($p = 0.001$), single support ($p = 0.003$) under complex three-step backward calculation conditions compared with the control, but not under the less challenging DT two-step forward calculation conditions
Mirelman *et al.* (2010)	Repeated measures design	TT with virtual obstacles. The VR simulation required obstacle negotiation in two planes, while continuing to walk on the treadmill. Comparison was made to a historical active control group who followed similar protocol of TT but without VR	18 sessions (three per week for 6 weeks)	20 participants with PD (mean age: 67.1 ± 6.5 years) moderately impaired but were able to walk unassisted for at least 5 min	Improvements in gait velocity and stride length under usual walking. However, under the dual-tasking, gait velocity ($p = 0.003$) and stride length ($p < 0.001$) were significantly higher after training with TT + VR compared with TT alone. Dual-task gait variability decreased and Trail Making Test times improved after TT + VR training

Note: CGI: Cognitive-gait intervention; DT: Dual-tasking; MMSE: Mini Mental State Examination; RCT: Randomized controlled trial; TT: Treadmill training; VR: Virtual reality. Adapted with permission from Segev-Jacubovski et al [56].

Table 2

Cognitive Pharmacotherapy for Balance, Gait and Fall Risk

Study (years)	Study design	Type of intervention	Duration of intervention	Participants	Summary of findings
Auriel *et al.* (2006)	Open-label, before–after design	Before and 2 h after taking a single dose of 20 mg of MPH	2 h	21 patients with idiopathic PD who receive l-Dopa, (mean age: 70.2 ± 9.2 years, MMSE: 28.8 ± 1.7)	Improvement in the Attention (p = 0.025), whereas the EF Index showed only a trend (p = 0.099). The Timed Up and Go (p = 0.001), gait velocity (p = 0.005) and stride time variability (p = 0.013) showed significant improvements
Ben-Itzhak *et al.* (2008)	RCT, double- blind, placebo-controlled	Before and 2 h after taking 20 mg MPH or a placebo	2 h	26 older adults without dementia with subjective memory complaints (mean age: 73.8 ± 1.2 years, mean MMSE: 27.8 ± 1.4)	MPH improved Timed Up and Go (p = 0.004), stride time variability (p = 0.03) and EF (p = 0.03); effects not observed after treatment with the placebo
Montero-Odasso *et al.* (2009)	Open-label study with controls	5 mg/day of donepezil for 1 month, and another 3 months with 10 mg/day. The MCI group with no treatment	Up to 4 months	Six patients with mild AD (mean age: 79.9 ± 4.8 years; MMSE: 22.3 ± 1.2; MoCA: 15 ± 1.4) compared with eight patients with MCI (mean age: 75.6 ± 6.2 years; MMSE: 27.9 ± 1.7; MoCA: 22.9 ± 1.7)	AD patients increased their gait velocity after 1 month under single (p = 0.045) and dual-tasking (p = 0.047). Stride time variability decreased (improved) during follow-up. These increases were maintained for 4 months. Gait measures in the MCI (control) group were worse than at baseline
Assal *et al.* (2008)	Before–after design	Galantamine mean dose of 17.8 ± 3.5 mg/day	24 weeks	Nine patients with mild- to-moderate AD (mean age: 77.9 ± 2.1 years; mean MMSE: 26.4 ± 5.2) compared with 18 no-treatment control subjects without dementia (mean age: 78.1 ± 1.0 years; mean MMSE: 29.4 ± 0.8)	Stride time was shorter under dual-tasking after treatment (p = 0.01). There was no change in the controls
Chung *et al.* (2010)	Randomized, crossover, double-blind	Donepezil compared with placebo. In each drug phase, subjects were instructed to take 5 mg/day of donepezil or placebo for 3 weeks and to increase to 10 mg/day for the remaining 3 weeks	6 weeks, 3 weeks washout, 6 weeks of placebo	23 patients with PD who reported falling or nearly falling (mean age: 68.3 ± 10.8 years; MMSE: 27.6 ± 4.5)	Less falls with donepezil than when taking placebo (p = 0.049). Subjects with the most falls at baseline tended to show the largest improvements. No differences in Activities of Balance Confidence Scale, Berg Balance Scale, UPDRS III or MMSE scores
Beauchet *et al.* (2011)	Before–after design	Memantine mean dose of 20 mg/day in the morning - titrated in 5 mg increments over 4 weeks	211.0±78.2 days	17 patients with AD (mean age 83.8±5.8 years; 52.9% women; MMSE at baseline: 14.5±4.2) and 32 age- and gender-matched control patients with AD without any anti-dementia drug (mean age 80.0±6.6 years; 56.3% women; MMSE at baseline: 23.2±5.3)	Stride time variability decreased (improved) during follow-up in the memantine group (6.3±6.1 versus 3.6±1.3, P=0.038)

Note: AD: Alzheimer's disease; EF: Executive function; MCI: Mild cognitive impairment; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; MPH: Methylphenidate; PD: Parkinson's disease; UPDRS: Unified Parkinson's Disease Rating Scale. Adapted with permission from Segev-Jacubovski et al [56].