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REVIEW ARTICLE

The neurobiology of falls

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Abstract Falling is a major clinical problem; especially, in elderly population as it often leads to fractures, immobilization, poor quality of life and life-span reduction. Given the growing body of evidences on the physiopathology of balance disorders in humans, in recent years the approach of research on falls has completely changed and new instruments and new definitions have been formulated. Among them, the definition of "idiopathic faller" (i.e. no overt cause for falling in a given subject) represented a milestone in building the "science of falling". This review deals with the new determinants of the neurobiology of falling: (1) the role of motor impairment and particularly of those "mild parkinsonian signs" frequently detectable in elderly subjects, (2) the role of executive and attentive resources when coping with obstacles, (3) the role of vascular lesions in "highest level gait disorder" (a condition tightly connected with senile gait, cautious gait and frailty), (4) the role of the failure of automaticity or inter-limbs coordination/symmetry during walking and such approach would definitely help the development of screening instrument for subjects at risk (still lacking in present days). This translational approach will lead to the development of specific therapeutic interventions.

Keywords Falls · Postural instability · Parkinsonism · Automaticity · Cognition · Freezing of gait · High-level gait disorder

Introduction

Annually, falls are directly or indirectly related to 1,800,000 admissions to emergency departments and 16,000 deaths [1], in the United States alone. Falls are the

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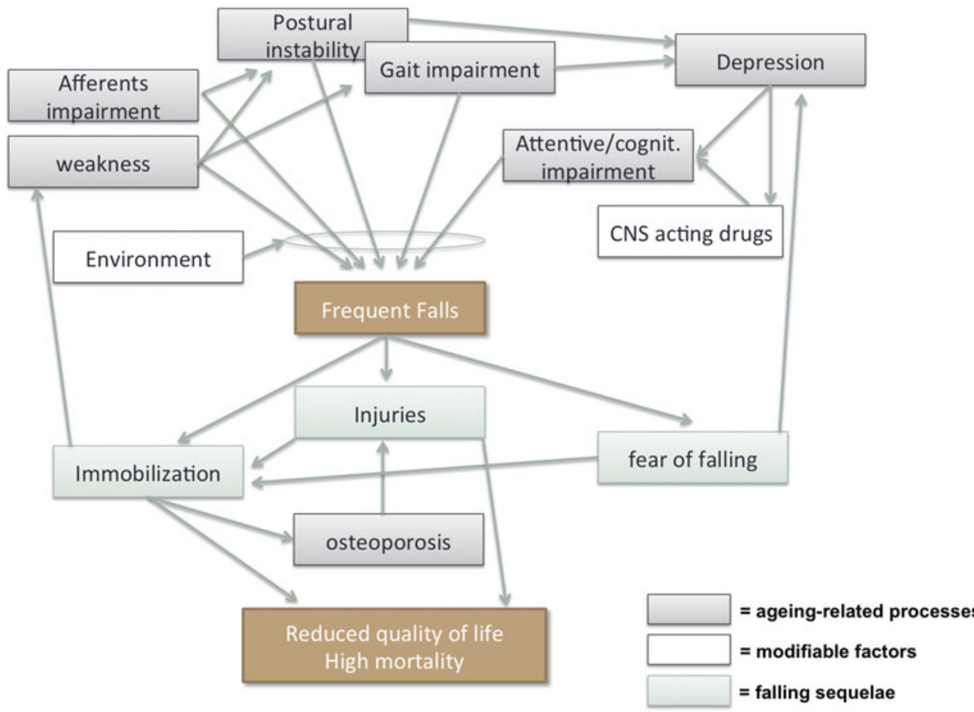

Fig. 1 A multifactorial process plays a complex role into the pathophysiology of falling. The *figure* shows the contribution of ageing processes, the few modifiable factors as well as the consequence of falling (modified from [67, 86])

leading cause of injury-related admissions to hospital in people of 65 years and over [2], leading to poor quality of life, immobilization and life-span reduction [3, 4]. Even a single non-traumatic fall may have a severe impact on the global health perception of a person. In addition, as a consequence of the psychological burden related to the fear of falling that can develop after falling, "active" avoidance from mobility and loss of independence are also frequently observed [3].

Many research publications were devoted to the topic in recent years. For example, PubMed search for the terms "falls" or "falling"—limited to humans and excluding reviews—yielded 19637 entries between the years 2000 and 2010. Yet so far the pathophysiology of falling is still far to be fully elucidated, mainly due to its multifactorial nature (Fig. 1). The risk of falling in a healthy subject over 65, who never fell is 27 % (95 % confidence interval: 19–36 %). The only strong predictor for a future fall is a previous positive history of falling [5], which is actually a paradox as it does not allow any primary prevention.

The studies on the limits of stability, i.e., the ability to reach beyond the base of support, represent a good example of the inconsistencies in research results on fall prediction. For example, while Wallmann observed no significant difference in mean functional reach distance between elderly non-fallers and fallers [6], Butler et al. [7] examined a larger cohort of elderly subjects and reported that fall rates were significantly associated with reach distance, in agreement with a previous study on voluntary postural sway [8].

The needs to better evaluate fall risk increased the interest on the neurological bases of postural control and, in more recent years, have driven the building of the "science of falls-prevention" [9]. The American Academy of Neurology concluded that specific conditions are level A (i.e. stroke, dementia and gait/postural instability impairment) or level B (i.e. Parkinson's disease—PD, neuropathies, lower limbs weakness and poor visual acuity) risk factors for falling [10]. This "disease-oriented" approach for defining levels of fall risk lacks however the understating of the pathophysiological core process causing falls and in particular the causal mechanisms leading to the actual occurrence of falls. Figure 2 depicts some examples of the difficulties in examining the relative contribution of the factors involved in the process leading to a fall. To this regard, a useful construct for speculative purposes is the identification of "idiopathic fallers", i.e. those subjects who fall in absence of any overt cause or underlying disease [11]. In fact, while falls are more prevalent in the elderly population as compared to young adults, the elderly population can still be subdivided into "(idiopathic) fallers" and "non-fallers". This categorization is based on the number of falls experienced by an individual in a given period of time (i.e. more than one unexplained fall in the year preceding an assessment [12]), and on the absence of any apparent reason for the falls, such as e.g. vestibular deficit.

Rather than dealing with specific nosological entities, the present review deals with those neurological features probably shared by many fallers regardless of their specific

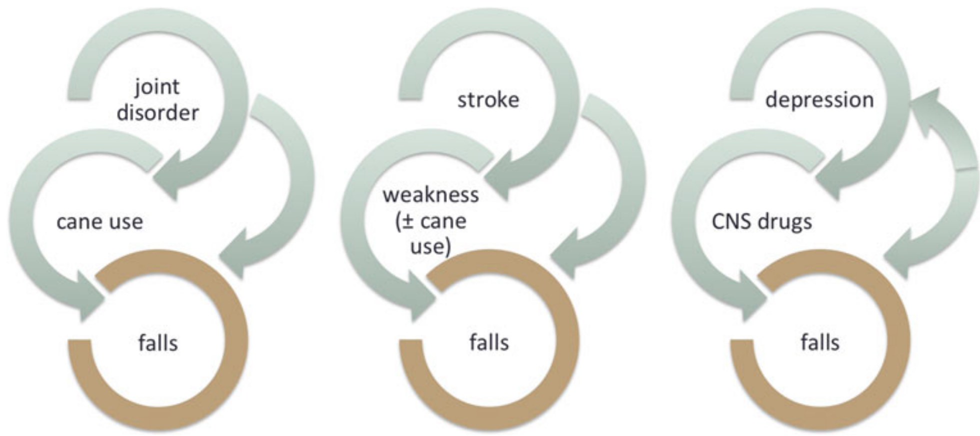

Fig. 2 Epidemiological studies can hardly establish the relative contribution of the factors associated with falling. The *figure* shows some examples of the complex interplay between them. For instance, depression is an established risk factor for falling, but it may also be a consequence of falling itself; moreover, subjects suffering from depression are usually treated with psychoactive drugs, which are also related to an increased risk of falling (see also Fig. 1). Given these considerations, "idiopathic fallers" represent an important population to study to define the mechanisms behind falling beyond the routine clinical grounds

diseases or associated conditions. In doing so, we will address four specific domains: the impairment of motor control or cognitive functions, the interface between motion and cognition as represented by the impairment of automaticity, and the subjective perception of the risk of falling. Therefore, we will not cover all the available data about the pathophysiology of falling, such as the impairment of the afferents systems (i.e. vision/hearing loss [13], proprioceptive [14], and vestibular [15] function) or more overt cause of falling (e.g. muscular weakness [16] or cerebellar ataxia [17]).

Motor impairment

The need for a harmonious modulation of trunk/ankle flexibility well explains why motor impairment (either weakens, slowness or poor coordination) increases the risk of falling under physiological perturbations (e.g. body sway during standing or walking) or after extrinsic destabilizing factors (e.g. during tripping). The rapid succession of strategies aimed at preserving body stability after a perturbation is schematized in Fig. 3: the initial one is the "ankle strategy", a motor plan characterized by the release of trunk muscles and stiffening of the ankle joint. When the perturbation is so severe or the ankle strategy is not efficient enough, the second motor plan is the "stepping strategy", during which the ankle joint is released and the subject performs one or more steps to enlarge the base of support. If these motor acts fail to preserve stability, the upper limbs play a major role in performing rescue strategies (e.g. holding on some support) or protective reactions (limiting the traumatic consequence of falling when it cannot be avoided). This model well explains: (1) the pathophysiological link between trunk inflexibility (worsened by rigidity [18] or fear of falling [19]—see below) and instability (i.e. ankle strategy), (2) the pathophysiological link between gait disorders and falling (i.e. "stepping strategy"), (3) the need for an adequate flow of information through visual, vestibular and somatosensorial afferents, (4) the need for attentive and executive resources to adapt to the environment and to the type and strength of perturbation by rapidly switching to one strategy to the other (Fig. 3).

The motor determinants of a frequent faller are characterized by a disorder of either the base of support or the center of body mass [20]. The most common disorder of base of support is freezing of gait (FOG), defined as the "episodic inability (lasting seconds) to generate effective stepping" [21]. Gait initiation, turning, spatial constraints and stress are known triggering factors for FOG [21], which is frequently presented by parkinsonian patients [21, 22] and represents a major cause of falls [23] and poor quality of life [24] for them. Patients with FOG usually fall forward because of the sudden perturbation of the base of support during ongoing walking and also because the stopped posture of these patients mechanically favor such direction [25]. Even during episodes of normal walking, patients with FOG have a pathological gait pattern [26] characterized by an impairment in rhythmicity [27], symmetry [28], bilateral coordination [29], step scaling [30] and dynamic postural control [31] (see below). Moreover, the cognitive profile of patients with FOG is characterized by the impairment of executive and attentive functions [32–34], thus representing another link between movement control and cognition (see below).

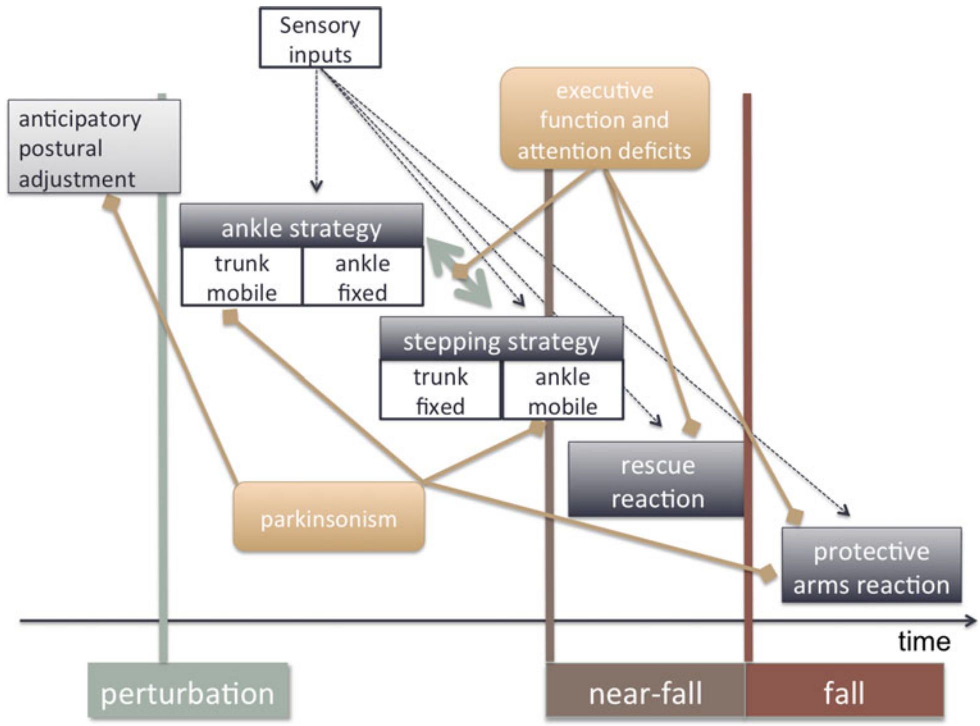

Fig. 3 The figure schematically shows the rapid succession of strategies aimed at preserving body stability after a single perturbation. When one or more stability strategies are impaired, perturbation leads to near-fall and, when also rescue reactions are not properly working, falling is an inevitable event (see text for details). Modified from [95, 96]

The typical disorder of the center of mass is postural instability, usually leading to an impairment along the anteroposterior axis, which is typically characterized by a backward body sway (also because the forefoot mechanically protects patients during forward perturbations). The impairment along the mediolateral axis is more specific to conditions characterized by overt postural instability, such as ataxia, atypical parkinsonism and Huntington's disease [35, 36]. Accordingly, force platform measurements recorded in laboratory settings disclosed that especially mediolateral movements of the center of pressure can provide useful information in predicting future falls and recurrent fallers [37].

Patients with parkinsonism manifest disorders of both the base of support and the center of body mass and therefore fall much more frequently than elderly subjects [5, 38, 39]. Other ageing processes not strictly confined to the dopaminergic systems play a major role in the pathogenesis of the axial impairment. Interestingly, in recent years, mild parkinsonian signs have been recognized in elderly subjects without PD [40, 41]. These patients present features recognized as risk factors for falling, such as an almost exclusive involvement of gait and postural stability [40, 41] as well as executive cognitive function [42, 43] (see below), eventually leading to an increased risk of mortality [43, 44]. The emergence of mild parkinsonian signs is related to vascular lesions mainly involving the frontal regions [45, 46]. Noteworthy, the leukoaraiosis and disability (LADIS) study has found an association between the risk of falling and vascular lesions within the frontal lobe [47].

Cognitive impairment

Although gait and postural stability are mostly automatic—i.e. subcortical—motor behaviors, cognitive—i.e. cortical—functions control the strategies employed for navigation and management of perturbations, thus preserving stability [48, 49]. The model shown in Fig. 3 also explains why cognitive and attentive problems impair the postural control at different levels. Our knowledge about the physiology of cortical control of stability in humans is quite limited. Apparently, the evolution of bipedal walking shifted postural control mechanisms to higher centers of the central nervous system (CNS), including the cerebral cortex [50]. Noteworthy, in Uner Tan syndrome, a rare autosomal recessive dysequilibrium syndrome, individuals fail to learn to walk bipedally in the absence of any sensory, vestibular or motor coordination defects; they walk on all four extremities, have a primitive language and rudimentary intelligence associated with severe spatial deficits [51], underlying the evolutionary interplay between cognitive development and high-bipedal postural stability performances related to humans.

Postural stability can be viewed as a strategy per se. As such, the CNS adapting to the environmental constrains should rapidly select the appropriate stabilizing strategy for each circumstance which evolves from postural perturbation, including a protective reaction when fall cannot be avoided. PD patients have a higher rate of injurious falls than elderly healthy subjects [52] and following this line of reasoning, the protective arm response during falling might be impaired not only due to parkinsonian bradykinesia, but also due to deficits of attentive strategies, thus leading to the inability to generate a well-organized protective motor response. The relevance of the protective arm response is also highlighted by the observation that elderly fallers with the combined fractures of distal radius and hip have a better prognosis than the peers with isolated hip fracture [53].

The research on dual task (DT), i.e. the abilities to perform a secondary task simultaneous to walking, has been driven by the observation that the failure to maintain a conversation while walking ("stop walking when talking") is a strong predictor of future falls [54]. DT abilities worsen due to the impairment of automaticity and attention secondary to subclinical processes. Even during standing, postural sway increases when a cognitive task is performed concurrently with a postural task [55], suggesting that constant dynamic control of postural adjustments during standing also requires certain level of attention resources, and when the latter are also consumed by simultaneous task, this control is compromised as expressed by inefficient postural adjustments resulting in "overshooting or undershooting", which lead to increased sway. Similarly, locomotion—another presumably "automatic" motor function—also requires certain level of attention resources. In fact, elderly people increase stride variability (suggesting reduced automaticity—see below) while performing a secondary task during walking [56]. This "DT cost" is higher among elderly subjects as compared to young adults [57]. Moreover, in patients with overt disease, such as stroke or PD, gait deteriorates even more during dual tasking [58–61]. It has been found that executive function and attention scores were lower in the PD patients with higher tendency to fall, as compared to non-fallers [61]. Another form of DT impairment is when elderly people fail to get their priorities right [62] (see below). Interestingly, general measures of cognition, e.g., memory, did not differ between the groups.

During daily life, subjects encounter many attention-demanding events. The evidences indicated here suggest that such events, which can be considered as daily life DT conditions (as opposed to the laboratory controlled DT conditions), pose high risk for gait deterioration in particular among subjects with reduced executive function. The involvement of cognitive control in normal gait could explain why falls are so common in patients with dementia and why demented patients are so vulnerable to DT performance while walking [63, 64]. Interestingly, PD patients with predominant axial impairment have a much greater risk of cognitive decline and dementia than patients with tremor-dominant disease [65]. The impairment of executive function can be the primary cause of falls in idiopathic elderly fallers [57, 66], well explaining also the high incidence of falls and injuries in individuals taking psychoactive medication [67]. Finally, evidences for the role of attention and cognition in postural control come from the side effects of drugs impairing cognition. On the other hand, donepezil—usually used for the treatment of dementia—has been recently found to significantly reduce falls rather than near-falls in patients with PD without cognitive impairment [68], thus indicating that the drug did not improve stability, but rather cognitive resources.

High-level gait disorder

High-level gait disorder (HLGD) [69] was the term utilized to solve the confusion and debate on "frontal gait disorder" or "gait apraxia" terms used by Sudarsky and Ronthal to describe 20 % of 50 elderly patients who came to their attention [70]. Nutt et al. referred to these gait disturbances as HLGD to signify dysfunction of the highest integrative sensorimotor systems with intact basic motor and sensory functions. In classifying these disorders, they mixed clinical phenomenology (gait ignition failure) with anatomical location ('frontal gait disorder'). The terminology used to describe and classify HLGD as well as the extent to which these entities are separate or overlap remain subject of debate and are beyond the scope of this review. However, it is important to recognize that all these conditions are clinically characterized by high-stepping variability (see below) [71] and postural instability [72]. The dysequilibrium of HLGD may have several causes including awkward trunk movements, poor control of trunk motion and impaired reflex control of posture, all which may lead to difficulty turning over, arising, standing, walking, turning and increased body sway [72]. In addition, FOG (see above) is frequently observed in HLGD, being associated with significant functional disability and a specific frontal cognitive disturbance of initiation [73]. In keeping with the LADIS study [47] and in research on mild parkinsonian signs [45, 46] (see above), in the majority of patients with HLGD diffuse vascular lesions of white matter are supposed to impair the communication between the basal ganglia and the supplementary motor area, a flow of information involved in the internal cueing and guidance of learned, skilled, motor acts of the limbs [74, 75].

Automaticity of posture and gait control and its relation to recurrent falls

As opposed to voluntary movements, the control of posture and locomotion, is mostly automated, i.e. pre-existing motor sets are being continuously activated to address dynamic postural perturbations [49] and to maintain gait patterns [76]. In general, poor automatic response to postural perturbations as quantified by sway dynamics is considered indicative for fall risk. The relation between motor automaticity and fall risk is also detected when inspecting human gait dynamics, i.e., the long-term temporal sequencing of the repeated stepping movements. Gait is essentially a periodic—i.e. oscillatory—movement and its rhythmicity is assessed by measuring its variability. In one of the early studies on the relation between dysrhythmic gait and fall risk, Hausdorff et al. [77] examined the hypothesis that increased gait variability predicts falls among community-living older adults77. In a prospective cohort study, 52 community-living over 70 ambulatory adults walked for up to 6 min at their normal pace while wearing force-sensitive insoles which collected the timing of the gait cycles. Stride time variability was twofold larger for the subjects who subsequently fell as compared to the subjects who did not experience a fall in the follow-up period. Additional studies followed and described the relation between recurrent falling and increased gait variability with various forms of measures used to quantify gait variability (for a review see [78]).

Bilateral coordination of gait and gait asymmetry (GA) are indexes addressing the automaticity of gait in the level of the relative timing of stepping between the two legs. GA has been traditionally measured in terms of spatial asymmetry by considering the ratio between right and left step lengths; in more recent years, the timing properties of the anti-phase activation of lower limbs during uninterrupted gait have been considered as a better index of neural control. Human gait is considered to be symmetric [79] with the relative timing of left–right stepping in anti-phase [76, 80]. Ageing deteriorates both features, which are even further worsened by PD [81]. DT leads to a further deterioration in GA, more severely in PD patients and elderly idiopathic fallers than healthy elderly subjects [82]. Similarly, DT was found to impair the ability to maintain left–right stepping anti-phasing in PD patients [83]. A recent study has focused on risk factors for falling in subjects with PD in the "ON" state (i.e., under the beneficial effect of anti-parkinsonian drugs), the typical condition under which these subjects are functioning in their daily living. Gait speed, gait variability, GA and bilateral coordination of legs were found to be worse in PD fallers in either usual walking or DT as compared to PD non-fallers; moreover, the DT effects on gait variability and bilateral coordination were greater among the fallers [61].

Reckless and fear of falling: a continuum

The observation that some patients may have a variable subjective perception of the risk of falling in spite of similar objective disabilities is another important issue. In fact, patients with the "fear of falling" syndrome [84] overestimate the risk of falling and actively limit their

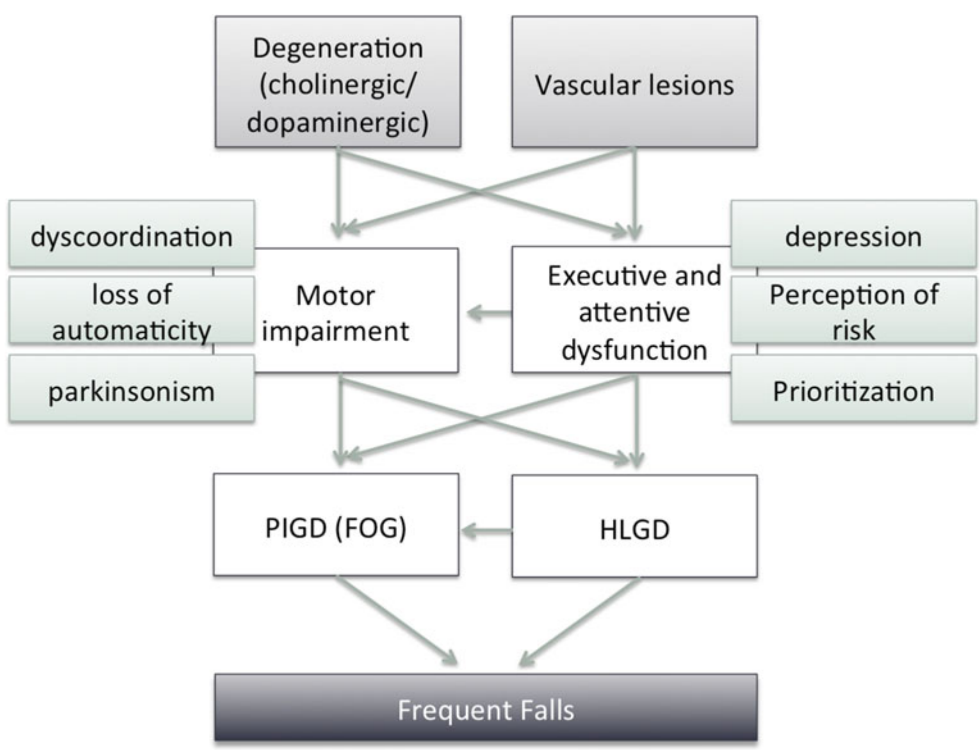

Fig. 4 The neurobiology of falling relies on specific features, shared by many fallers regardless of their clinical conditions. *FOG* freezing of gait, *HLGD* high-level gait disorder, *PIGD* postural instability gait disturbance

mobility; this may follow a near-fall and more often a fall, even if this should not necessarily be injurious. Up to 50 % of elderly people feel to be unsteady [85]; more importantly, they cannot get up unassisted from the floor [86]. Therefore, elders sometimes wait hours prior to be assisted after a fall, with a consequent psychological constrain. Fear of falling is not only a risk factor for renewed falls [87], it may also lead to secondary immobilization with all its related adverse consequences [88]. The appropriately cautious gait (also reported in HLGD) should be distinguished from the incapacitating "fear of falling" producing an inappropriately cautious gait. In contrast, other subjects (often with dysfunction of frontal lobe, as seen in atypical parkinsonisms, e.g. progressive supranuclear palsy) underestimate the risk of falling in spite of their severe postural instability. This "motor recklessness" [89] leads to injury-risk behaviors, further increasing the risk of falling.

The recognition of a functional domain evaluating the risk of falling is not a trivial concept and allows the understanding of other phenomena. For example, while walking under complex circumstances, young healthy people neglect secondary tasks and lend more priority to safety; this prudent "posture-first" strategy is diminished in elderly people [59, 62], and failure to prioritize gait under difficult circumstances is also associated with falls [62].

Conclusions

In conclusion, this review has summarized the determinants of the neurobiology of falling, showing the complex interplay between several factors: the motor impairment (particularly the role of parkinsonism), the decline of executive and attentive resources, and the interface between them, represented by the impairment of automaticity or inter-limbs coordination/symmetry during walking.

The recognition of a neurobiology of falls (Fig. 4) is the first step towards the definition of specific therapies. The loss of thalamic cholinergic markers as detectable in vivo by PET, presumably because of loss of cholinergic projections from pedunculopontine nucleus (PPN), has found to correlate with falls in patients with PD [90, 91]. Such observation opens new avenues for symptomatic treatment using cholinergic agents [68] or deep brain stimulation of PPN [92]; whether, these strategies improve stability or compensations (e.g. increasing alertness) is still unknown. Similarly, other therapies aimed at improving attentive resources (such as methylphenidate [93]) or cortical metabolism (such as extradural cortical stimulation [94]) are currently under evaluation. In the next future, the findings of the "science of falls-prevention" will certainly be translated into clinical practice.

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