Emerging therapies for gait disability and balance impairment: promises and pitfalls

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Abstract

Therapeutic management of gait and balance impairment during aging and neurodegeneration has long been a neglected topic. This has changed considerably during recent years, for several reasons: (a) an increasing recognition that gait and balance deficits are among the most relevant determinants of an impaired quality of life and increased mortality for affected individuals; (b) the arrival of new technology that has allowed for new insights into the anatomy and functional (dis)integrity of gait and balance circuits; and (c) based in part on these improved insights, the development of new, more specific treatment strategies in the field of pharmacotherapy, deep brain surgery and physiotherapy. The initial experience with these emerging treatments is encouraging, although much work remains to be done. This narrative review aims at discussing several promising developments in the field of gait and balance treatment. We also address several pitfalls that can potentially hinder a fast and efficient continuation of this vital progress. Important issues that should be considered in future research include a clear differentiation between gait and balance as two distinctive targets for treatment, and recognition of compensatory mechanisms as a separate target for therapeutic intervention.

Introduction

The therapeutic management of gait disability and balance impairment has long been a neglected topic, presumably because these two axial symptoms – despite being common and often devastating – were perceived as being largely untreatable. However, gait disability and balance impairment have become exciting topics in recent years, for all, clinicians, scientists and health policy makers, for a variety of reasons. First, there is growing recognition that gait disability and balance impairment are among the most relevant determinants of an impaired quality of life[1-5] and an increased mortality[6, 7]. Second, new technology such as advanced structural[8] and functional brain imaging[9] (often using mental simulation of action to study gait and balance while lying recumbent in the scanner[10, 11]) have become available, allowing for accurate measurements of the brain anatomy and cerebral activation patterns related to gait and balance. Finally, new treatment approaches are beginning to see the light, including pharmacotherapy, deep brain stimulation and physiotherapy, with encouraging initial results.

Our main aim here is to offer the reader a "bird's eye perspective" of the various opportunities and difficulties that are associated with these therapeutic developments for gait and balance deficits (Table 1). This makes it necessary to describe therapeutic studies relevant for this review in a relatively condensed form; we refer to Table 2 for further details. In addition, specific interventions will be addressed by other papers in this volume. We will focus mainly on developments in the field of Parkinson's disease (PD) because the evidence is most abundant for this condition, but we will mention other neurodegenerative diseases whenever this is relevant.

Promising developments and opportunities

Increasing focus on gait and balance in drug trials

Many previous clinical trials failed to address gait and balance problems adequately, in part because of a lack of interest, but also in part because good outcome measures were lacking. For example, in the field of PD, clinical trials at best used a set of the gait and balance items that were scored routinely as part of the Unified Parkinson's Disease Rating Scale (UPDRS). However, many of these items represent only crude measures of gait and balance disability, and are subject to variations in clinical performance and interpretation[12].

This situation has changed in recent years, and several drug studies have focused specifically on potential improvements in gait or balance. For example, freezing of gait (FOG) is now widely recognized as an important cause of falls in the field of PD[13, 14] , and the advent of better clinical

outcomes – including detailed questionnaires[15] and clinically based tests such as rapid turning on the spot[16, 17] – has permitted better study of this intriguing phenomenon. A series of drug studies has focused specifically on FOG and, taken together, it is becoming clear that dopaminergic medication (in particular levodopa[18, 19] but also monoamine oxidase inhibitors such as rasagiline[20]) can at least partially alleviate OFF state FOG for most patients , despite rare cases where levodopa can worsen this symptom when it occurs in the ON state[21].

Other studies have benefited from the advent of quantitative electrophysiological outcomes as objective surrogate for the clinical scores. Examples include the use of electromyography or kinematic analyses for the quantitative assessment of gait, in patients walking either on stationary surfaces or on motorized treadmills. These techniques have also been used to objectively study balance, in patients standing either on a stable support surface ("static posturography") or on a movable support surface ("dynamic posturography")[22]. Inclusion of such objective parameters in clinical studies has helped to generate new knowledge about the influence of old and new drugs on gait and balance disabilities. For example, various studies have used posturography techniques to test the effects of dopaminergic medication on quantitative sway parameters in PD, showing that some elements of affected postural control are partially dopa-responsive, although most others are dopa-resistant or even induced by dopaminergic medication (see e.g. [23-25]).

One relevant consequence out of these studies (but also from functional studies [26]) was that the dopaminergic system could no longer be held primarily responsible for axial function and deterioration, underscoring the need for development of non-dopaminergic drugs. Examples are methylphenidate and dihydroxyphenylserine (DOPS), which have been tested as potentially promising drugs to improve gait because of their primarily noradrenergic properties. The noradrenergic system including the Locus coeruleus is affected e.g. in PD and progressive supranuclear palsy (PSP), and closely correlated to axial symptoms (for a review see [26]). This nucleus is located, adequate for its coordinator function, in the brainstem and projects to widespread areas in the CNS, including the cortex, cerebellum and the spinal cord. Methylphenidate has recently been tested in a large, double-blind RCT where gait was the prime outcome[27], illustrating how important axial motor deficits are becoming. In this study (which involved advanced PD patients who had previously received subthalamic nucleus stimulation), gait hypokinesia and freezing improved with methylphenidate during an observation period of 90 days. A positive effect in particular on gait, retropulsion and festination in patients with Parkinsonism based on the clinical impression of a neurologist has been observed in a large dose-finding study with L-threo-DOPS[28], however others did not find such an effect[29], and the clinical relevance is still unclear[20].

Another non-dopaminergic target that has received much attention is the central cholinergic system, which includes among others the pedunculopontine nucleus in the dorsal mesencephalon. Compelling new evidence from both neuroimaging studies (fMRI and PET studies) and postmortem work has shown that this cholinergic system is crucially involved in gait and balance regulation (see e.g. [30, 31]). In more detail, the pedunculopontine nucleus is involved in postural adjustments[32], and can thus be seen as a critical coordinating point for (or between) balance and gait. These new insights have stimulated clinical trials in which the effect of cholinesterase inhibitors were tested, using an axial motor symptom as the primary outcome measure. For example, in a controlled study in PD patients, a 6-week treatment with donepezil led to an almost 50% reduction of falls compared to placebo[33]. Although the main outcome of this study – the number of falls – does not reveal whether donepezil improves gait, balance or even cognitive functions associated with falls (e.g. attention), this study did serve as a promising starting point for further and more specific intervention studies.

Increasing focus on gait and balance in neurosurgical trials

Neurosurgical studies are also aiming increasingly on gait and balance deficits as primary targets for improvement. Some studies have evaluated the effects of subthalamic or pallidal deep brain stimulation as a possible new approach to treat gait and balance deficits, while others aimed to understand why axial motor control can worsen in a subgroup of patients following surgery. Many of these studies used quantified treadmill walking or balance performance during a posturography experiment as outcomes. The overall impression is that both subthalamic and pallidal deep brain stimulation can improve gait (including FOG) if this was dopa-responsive prior to surgery, while balance deficits are largely resistant to, or even worsen after deep brain stimulation (see e.g. [34-36]).

Stimulated by the aforementioned new pathophysiological insights, attention has shifted more recently towards stimulation of other targets to improve gait in patients with advanced PD, including the pedunculopontine nucleus[37, 38] and the substantia nigra pars reticulata[39]. There is increasing evidence supporting an integrative role on locomotion also of the latter area[40]. Particularly for these innovative and 'high-risk' treatments, sensitive and quantitative outcomes are very helpful to understand whether or not any therapeutic effects have occurred. For example, a subtle gait improvement that is captured only by electrophysiological assessment may not be clinically relevant if it is not substantial enough to be identified also by the clinical eye. However, such a subtle improvement could be important as 'proof of concept' that the new approach is at least affecting the symptom under study. Indeed, the effects of pedunculopontine nucleus stimulation have thus far

been largely disappointing, and careful assessment of gait changes following stimulation of different targets within the dorsal mesencephalic locomotor region will be needed to identify the best area (if any) to improve axial disability.

Increasing focus on gait and balance in allied health studies

The quality of intervention studies in the field of allied healthcare has improved considerably during recent years, and some trials in patients with PD have shown convincing effects on gait and balance deficits for specific allied health interventions. Both the number and the quality of the intervention studies in this field are improving steadily, in particular for physiotherapy[41]. Evidence is strongest for external cueing, a specific physiotherapy intervention aimed to improve gait and alleviate FOG, and for which there is now class II evidence (see e.g. [42-44]). Also well studied is treadmill walking: a Cochrane review suggested that this improves gait speed, stride length, walking distance and health-related quality of life in PD patients [45]. Another Cochrane review concluded that group and home-based exercise programs, as well as home safety interventions delivered by an occupational therapist, can help to reduce the risk of falling in community dwelling elderly[46]. Nordic walking is also a popular intervention, both among clinicians and patients. It can positively influence gait speed[47] and qualitative gait parameters such as stride length and gait variability[48]. Further promising approaches are high-amplitude movements (LSVT®BIG technique)[49], dancing[50], movement strategy training or musculoskeletal exercises[51] and Tai Chi[52].

Cognitive training is a particularly interesting approach, as both gait and balance relevantly depend on (proper) cognitive function. In one study, after a 4 weeks task-specific dual tasking - gait training program, PD patients showed improved gait speed and gait variability during dual tasking[53]. Another study[54] aimed to promote the development of new motor and cognitive strategies for impaired obstacle navigation (which is an important cause of falls in the elderly[55]) in PD patients. They received progressive treadmill training and, in parallel, virtual obstacles. Gait speed, stride length, gait variability and stride time improved in single and dual tasking conditions, as well as during over-ground obstacle negotiation[54]. Results from cognitive training interventions in e.g. individuals without neurodegenerative diseases[56, 57] and ataxia[58] support the usefulness of cognitive training for the improvement of gait and balance deficits.

Occupational therapy is another potentially useful intervention, for example via removal of domestic hazards. However, current evidence is less robust in this field (class III), although new, large and well-designed studies are now underway[59].

Growing interest from private companies to build supportive tools

Another promising development is the mounting interest from the private business sector in developing assistive tools for gait and balance deficits. This has led to a rapidly increasing variety of assistive devices that can benefit affected patients. Straightforward examples are watches with alarms to remind when to take medication and to record medical history, and, more specific, hi-tech eye-glasses with LEDs, where patients see e.g. a checkerboard grid in front of them and step over the patterns. Wheeled rollators are being improved, for example by adding an automatic brake (to prevent festination in patients unable to use the normal manual brake) or by adding visual cues such as a laser light (that projects onto the floor in front of the subject) to overcome FOG episodes[60]. These assistive devices can be used for symptomatic treatment, and enable an extended, safer and more effective mobility for users.

Ambulatory monitoring devices and domestics

As was pointed out before, history taking and physical assessment of gait and balance remain imprecise, subjective, at best semi-quantitative and thus prone to bias. A clear example is the pull test, which is routinely included within the Unified Parkinson's disease rating scale for the assessment of balance[61]. Treadmill walking, posturography and other objective electrophysiological assessments offer only a partial alternative, because the laboratory is an artificial environment. Findings obtained here may be reliable, but are often hard to translate to daily clinical life (limited ecological validity). These considerations have stirred a rapidly growing interest in the development of wearable and home-based technology, that combines several advantages: quantitative and objective outcomes; ability to measure longitudinally; greater efficiency (compared to time-consuming hospital visits); and ecological validity[12]. Various approaches exist, ranging from lightweight body-worn sensors (goniometers or accelerometers) to home-based assessments (e.g. cameras to monitor navigation patterns in and around the house). Several such techniques have now been validated for the assessment of gait and balance impairment[62]. Interestingly, these devices can provide additional information about important parameters that are now usually not available for users or their health professionals, e.g. activity-related energy expenditure[63, 64] or sleep behavior[65]. We expect this field to advance quickly by clever exploitation of the potential offered by smartphones, with their built-in accelerometers and easy connection to the worldwide web. The first applications are beginning to find their way into clinical practice[66].

Pitfalls of current therapeutic management

The previous paragraphs highlighted the tremendous advancements in the understanding and treatment of gait and balance deficits. We now pinpoint some of the most relevant challenges that

can potentially hinder an efficient progress in the development of therapeutic strategies for gait and balance difficulties (Figure 1).

Lumping gait and balance disabilities despite different pathophysiologies

A general problem is the tendency in the clinical and scientific field to lump deficits in gait, balance and even postural alignment under one umbrella term, e.g. by referring to their joint appearance as "axial disability" or "Postural Instability and Gait Difficulty" (PIGD) signs. This approach is partially defendable because "clinically detected abnormalities of gait or balance" – without further division – are the most consistent predictors of future falls[67]. Falls can thus be considered as a marker of axial motor signs, and falls are therefore frequently used as a reasonable surrogate outcome parameter in therapeutic trials aiming to alleviate axial motor deficits. Indeed, falls have been identified as one of the four relevant milestones of advanced PD, with a mean time from occurrence to death of approximately 4 years[68]. In addition to searching for possible distinct properties in pathophysiology and affected neural circuitries for gait and balance, it will be equally important to search for joint pathologies. This search is particularly relevant in the context of higher locomotor functions (e.g. transitions and axial turns), and also in the context of falls which typically result from a complex interplay between gait and balance disability. Moreover, we have to consider that strict differentiation between gait and balance may not help decoding the term "dynamic balance", i.e. the adaptation of locomotion during initiation of gait, turning and avoiding obstacles, and (both voluntary and involuntary) stopping. Even FOG can be seen as a phenomenon of impaired coupling between balance and locomotor components[69]. Although variability of gait[70] and center of mass position relative to the front foot[71] may be useful markers of dynamic balance, many aspects remain that are not well understood.

Still, lumping also leads to loss of valuable information. Let's consider two examples. First, when a particular therapeutic intervention (e.g. multifactorial intervention strategies[46]) leads to a reduced rate of falls, it remains unclear whether and how each of the specific axial motor signs contributed to the observed effect. Second, in deep brain surgery trials, the summary score for PIGD signs is commonly used as outcome[72, 73]. Despite generally disappointing improvements in the overall PIGD summary score for all axial symptoms, some specific features may have responded well (e.g. cadence, gait velocity, stride length or step asymmetry[74, 76]) whereas others failed to respond or even worsened (e.g. righting responses to the retropulsion test[76]).

Another good reason NOT to lump all axial features is the fact that the underlying pathophysiology and prognosis of the various gait and balance deficits are very different. Compared to gait (which is a

pro-active process), keeping balance is mainly a reactive, corrective, or even explorative process[77]. Moreover, studies using functional neuroimaging have shown that the cerebral regions involved in gait control differ at least partly from those involved in keeping balance. Specifically, it has been suggested that two types of locomotion networks exist, with complementary responsibilities to organize gait: one for non-modulatory execution (involving precentral and cerebellar areas, as well as central pattern generators in the spinal cord), and another for planning and modulation of locomotion (supplementary motor area, basal ganglia, subthalamic and mesencephalic locomotor regions)[11, 78, 79]. In contrast, functional imaging studies in PD[30] and PSP[80, 81] have associated balance deficits with thalamic and frontal dysfunctions. We realize that methodological differences across studies may partially explain these observed contrasts in neural circuitries, but it seems likely that the cerebral organization is different for gait and balance.

Another argument not to lump gait and balance is the observation that these signs not always co-occur in individual patients. In the elderly population and in many neurological disorders (e.g. PD or cerebellar ataxia), gait disturbances are more common – and appear earlier – as compared to balance deficits[82, 83]. The opposite happens in PSP, where balance problems are the hallmark sign in early disease stages, even when gait is normal or only mildly impaired. This discrepancy again suggests a different underlying pathophysiology. Moreover, balance deficits appear more closely associated with (regular) falls than gait disturbances which, in turn, are associated with a poorer prognosis in PD[84].

The differential response to treatment also suggests that gait and balance are organized differently. In PD, the various axial symptoms respond differently to medical treatment. For example, various gait parameters[85], including most forms of FOG[19] are at least partially levodopa-responsive, but balance impairment is usually not[86]. A recent study of deep brain stimulation in PD patients found an improvement of FOG but not of balance parameters[39]. This all argues for relevant differences in underlying cerebral organization across the various axial symptoms. We therefore recommend that future studies address gait and balance separately, using dedicated outcomes for each of these axial signs.

Failure to accommodate compensatory mechanisms

During normal aging[87] and in the course of neurological disorders such as PD[88] and Alzheimer's disease[89], the primary neurodegenerative process activates compensatory mechanisms within brain circuitries that are initially spared. These compensatory mechanisms help to minimize or even suppress behavioral impairments. This may be particularly true for automated movements[90]. As

recently shown for both gait[91] and balance[92], compensated deficits then only become visible when the system is maximally challenged, for example by adding a complex secondary task while patients are walking or balancing. These examples illustrate the high capacity of compensatory mechanisms to counteract respective primary deficits. It is interesting to speculate about the possibility of training or improving these compensatory mechanisms, in addition to the current mainstay of treatment that merely aims at correcting the primary deficit[93]. This is an intriguing concept because compensatory neural pathways are not – or at least less – affected than the primarily affected system, and thereby conceivably have a higher probability to respond to (further) training than a system that has lost even the ability to perform its usual mission. Some currently available treatments already purposely exploit the compensatory abilities of the brain, the best example being external cueing techniques to improve gait[42, 94]. External cues - stimuli associated with the initiation and ongoing facilitation of a movement - help to restore motor behavior by influencing (also) non-dopaminergic neural networks associated with gait dysfunction[94-96].

Other interventions may have incidentally trained compensatory strategies, an example being aerobic physical exercise which is increasingly tested as a way to drive adaptive cerebral plasticity and thereby reduce gait and balance deficits[97]. It remains unknown just how aerobic exercise "works", but it likely offers a generic drive to the brain so training of primary deficits cannot be entirely disentangled from training of the various compensation mechanisms. Other treatments could focus more specifically on supporting the compensatory cerebral mechanisms. With the advent of detailed structural and functional neuroimaging, the nature of these compensatory circuitries is rapidly being unravelled, not only in patients with overt disease[98, 99] but also in the preclinical phase[100, 101]. Future work could examine whether gait and balance can be improved by targeting such compensatory circuitries directly, via transcranial magnetic stimulation or epidural electrical stimulation (for cortical targets), via deep brain stimulation (for deeper targets) or via transcranial direct current electrical stimulation.

Additionally, training can be focused on behavioural adaptation as a way to compensate for gait and balance deficits. A striking example is the ability of many PD patients to ride a bicycle, even in the face of severe and incapacitating gait deficits[102]. Cycling is a very different motor behaviour than walking, but it does restore the patient's independence and ability to travel. Examples of such compensatory behavior are abundant, and it is impressive to see the creativity of patients in finding effective solutions to cope with their disability. Identifying and supporting such solutions is a potentially useful supplement to the traditional approach of treating the primary disease deficits.

A conceivable advantage of targeting compensatory strategies for intervention of gait and balance deficits is the sustainability of the learned programmes because participants help to co-create an influenzable training effect on their symptoms, and this self-engagement may motivate patients to take responsibilty for continuing with their training. The relevance of this issue is discussed below.

Failure to promote physical activity

The clinical significance of current physiotherapy programmes with prolonged follow-up is often unclear or even doubtful[45, 103, 104]. This is possibly due to the fact that these programmes are not designed to structurally change behavior and to "induce" a sustained active lifestyle. Reversing the sedentary lifestyle of elderly subjects[105] and patients with neurodegenerative disorders[106] could have beneficial effects on gait and balance, achieve generic health benefits and increase survival[105, 107, 108]. However, motivating a sedentary person to become more active even in the long term is a challenging task, and complex interventions that include behavioral change programmes may be necessary to achieve this goal[109]. A recent example is the randomized controlled ParkFit trial, which evaluated the effect of a multifaceted behavioral change programme on physical activities in 540 sedentary PD patients over a period of 24 months. The primary outcome (LASA physical activity questionnaire) did not differ between the intervention group and controls, but the secondary outcomes (including both subjective and objective measures of daily activity and physical fitness) showed significant benefits for the treatment group that persisted for two years[110]. There were no adverse effects, in particular no cardiovascular complications or increase in falls. These results are far from final, but certainly justify further in-depth exploration of the merits of such behavioural change interventions. The challenge is to promote patient engagement and self-management, such that even elderly patients become (and remain) motivated to overcome their gait and balance deficits. It will be essential to develop physical activity programs that patients can incorporate into their daily routines, for example by allowing them to follow the program at home. Treatment compliance seems to be much higher, sustained and effective for domestic interventions as compared to interventions based in the lab, hospital or even the fitness school[111-113]. A promising new development is the use of gaming to induce sustained changes in behaviour[114], for example by changing the act of exercise into a naturalistic game (exergaming). The potential of this training is based on the feeling of "being there", followed by greater distraction, enhanced enjoyment and reduced tiredness[115].
In the long-term, self-management will become essential as a gratifying and economically attractive therapeutic approach to reduce gait and balance deficits.

Conclusion

Owing to recent developments in the basic understanding and diagnosis of gait and balance disability, these conditions are no longer perceived as being largely incurable. The positive results of specific therapeutic interventions that were based on new insights confirm this change in perspective, and create hope for further progress in the treatment of gait and balance deficits. However, researchers and clinicians have to be aware of several challenges that may hinder these advancements. We have discussed some of these in this review, including the disadvantage of lumping deficits in gait, balance and posture under one umbrella term, as well as the opportunities offered by exploiting compensation mechanisms as a novel therapeutic target. Moreover, we have argued that gait and balance deficits are negatively influenced by the sedentary lifestyle that is typical for patients with mobility deficits, and we have highlighted that strategies to increase motivation and self-engagement create new opportunities to achieve a more active lifestyle and treatment compliance. Taken together, this forms the basis for further development of multifaceted intervention strategies aimed at alleviating the disability resulting from gait impairment and postural instability.

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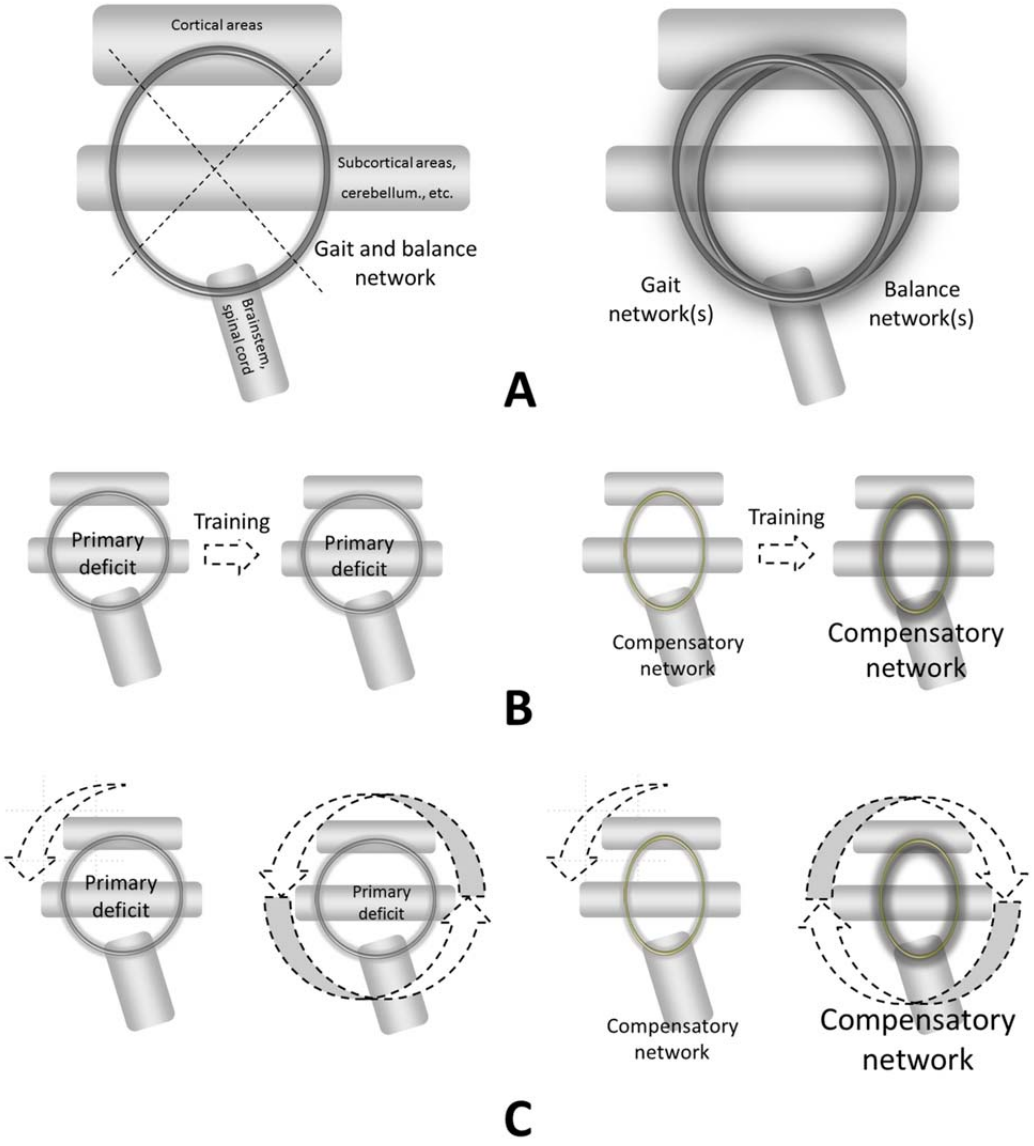
Figure 1



Relevant challenges that could hinder an efficient progress in the development of therapeutic strategies for gait and balance difficulties, including potential solutions. (A) Cerebral regions involved in gait control are not identical to those involved in balance control. They differ at least partly from each other. Moreover, it is probable that, for both gait and balance control, more than one network exists. (B) Training (indicated by dashed arrows) of the primary deficit is often unsatisfactory, so why not better train the compensation mechanisms involved? Compensatory mechanisms conceivably have a higher probability to respond to (further) training than a system that has lost even the ability to perform its usual mission. (C) A physically active lifestyle is obviously the most important factor to prevent from gait and balance deficits, and to have a good outcome if these deficits occur. However, current physiotherapy programmes (indicated by the dashed curved arrows) are short-lasting, and not designed to structurally reverse sedentary lifestyle behavior and to motivate to self-management and keeping active. Here, complex interventions for therapy of deficits as well as training of compensatory mechanisms that include behavioral change programmes are necessary.

Table 1

Promises	Increasing focus on gait and balance in drug and neurosurgical trials
	Increasing focus on gait and balance in allied health studies
	Growing interest from private companies to build supportive tools
	Advanced development of ambulatory monitoring devices and domestics
Pitfalls	Lumping gait and balance disabilities despite different pathophysiologies
	Failure to accommodate compensatory mechanisms
	Failure to promote physical activity

Table 2

Treatment regimen	Participants	Assessment	Axial outcome parameters	Reference
Medication				
Levodopa, ON and OFF condition	10 PD patients	Force platform	Sway parameters	Beuter 2008
	19 PD patients in	Video observation	FOG occurrence and duration	Schaafsma 2003
Methylphenidate, 90 days, RCT	79 PD patients with STN stimulation	Stand-walk-sit test	Change in number of steps	Moreau 2012
L-threo-DOPS, 4-6 weeks, dose-finding	168 patients with Parkinsonism,	Clinical impression	Occurrence / severity of motor symptoms	Narabayashi 1987
Donepezil, 6 weeks, RCT cross-over design	23 PD patients	Falls reported on postcards	Number of falls or near falls	Chung 2010
Surgery				
STN stimulation, ON and OFF condition	14 PD patients, 18 controls	Dynamic posturography	COM displacement after backward perturbation	Visser 2008
PPN stimulation after 3-6 months	6 PD patients	UPDRS	Gait and postural items	Stefani 2007
PPN stimulation after 12 months	5 PD patients	Optoelectronic system	Gait velocity, angular variables of large joints	Peppe 2010
(STN +) SNr stimulation, RCT cross-over design	12 PD patients	UPDRS	Axial items	Weiss 2013
STN stimulation, ON and OFF condition	8 PD patients, 12 controls	VICON® motion capture system	Gait symmetry	Johnsen 09
STN stimulation, ON and OFF condition	14 PD patients, 20 controls	Multivariate assessment including the SwayStar™ system	Trunk sway tremor during stance, trunk pitch velocity during transitions, roll stability	Vrancken 2005
Allied health				
Cueing training at home, 3 weeks, RCT	153 PD patients	UPDRS	Gait and postural items	Nieuwboer 2007
Walking with / without external or internal cueing	50 PD patients	Footswitches	Walking speed, stride length, step frequency, stride symmetry, double limb support	Rochester 2012
Walking with / without rhythmic auditory cues, open-label	29 PD patients, 26 controls	Force-sensitive insoles	Gait speed, stride and swing time variability	Hausdorff 2007
Treadmill training associated with auditory and visual cues, 4 weeks, open-label	40 PD freezers	Multivariate assessment	FOGQ, 6MWT, gait speed, stride cycle	Frazzitta 2009
Laserlight cues, 1 month, open-label	26 PD freezers	Multivariate assessment	FOGQ, falls frequency	Donovan 2011
Nordic walking, 4 weeks, open-label	19 PD patients	Multivariate assessment	Timed 10-m walking, TUG, 6MWT	Van Eijkeren 2008
Nordic walking, 6 months, RCT	90 PD patients	UPDRS, BBS, treadmill equipped with force platforms	postural stability, stride length, gait pattern and variability	Reuter 2011
LSVT® BIG*, 4 weeks, RCT	60 PD patients	Multivariate assessment	Timed 10 m walking, TUG	Ebersbach 2010
Tango dancing, 2 weeks, open-label	14 PD patients	Multivariate assessment including an instrumented, computerized walkway	BBS, gait velocity, step length, single support time, TUG, 6MWT	Hackney 2009
Movement strategy training, 2 weeks, RCT	28 PD patients	Multivariate assessment	Timed 10-m and 2 min walking, TUG, sway item of the UPDRS	Morris 2009
Tai Chi, 24 weeks, RCT	195 PD patients	Dynamic posturography	maximum excursion and directional postural control	Li 2012
Dual task training while walking, 4 weeks, open-label	7 PD patients	Foot insoles	Gait speed, gait variability under dual tasking situation	Yogev-Seligmann 2011
Treadmill training with virtual obstacles, 6 weeks, open-label	20 PD patients	GaitRite® and wearable sensor	Gait variability under dual tasking situation	Mirelman 2011
Dance video gaming, 12 weeks, RCT	31 older adults	GaitRite®	Gait velocity, cadence, step time, support time, step length	Pichierri 2012
Video game–based coordinative training, 8 weeks, intraindividual control design	10 children with progressive spinocerebellar ataxia	Dynamic gait index, VICON® motion capture system	Step variability, lateral sway	Ilg 2012
With/without use of a laser attached to a 4-wheeled walker	6 PD freezers	Walking a standardized course	Gait velocity, freezing episodes	Van Gerpen 2012

Relevant data of therapeutic studies that were mentioned in the text, investigating the effect of medication, surgery and rehabilitation on gait disability and balance impairment. Note that these interventions represent mere examples of studies that used quantitative outcomes to better understand the effects of dedicated interventions on gait and balance, but this table does not offer a comprehensive overview of all possible therapeutic options. 6MWT, 6-minute walk test; BBS, Berg Balance Scale; FOG, freezing of gait; FOGQ, FOG questionnaire; PD, Parkinson's disease; PPN, pedunculopontine nucleus; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; TUG, timed get-up-and-go test. * Intensive exercising of high-amplitude movements.