



## Consensus Paper: Ataxic Gait

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### Abstract

The aim of this consensus paper is to discuss the roles of the cerebellum in human gait, as well as its assessment and therapy. Cerebellar vermis is critical for postural control. The cerebellum ensures the mapping of sensory information into temporally relevant motor commands. Mental imagery of gait involves intrinsically connected fronto-parietal networks comprising the cerebellum. Muscular activities in cerebellar patients show impaired timing of discharges, affecting the patterning of the synergies subserving locomotion. Ataxia of stance/gait is amongst the first cerebellar deficits in cerebellar disorders such as degenerative ataxias and is a disabling symptom with a high risk of falls. Prolonged discharges and increased muscle coactivation may be related to compensatory mechanisms and enhanced body sway, respectively. Essential tremor is frequently associated with mild gait ataxia. There is growing evidence for an important role of the cerebellar cortex in the pathogenesis of essential tremor. In multiple sclerosis, balance and gait are affected due to cerebellar and spinal cord involvement, as a result of disseminated demyelination and neurodegeneration impairing proprioception. In orthostatic tremor, patients often show mild-to-moderate limb and gait ataxia. The tremor generator is likely located in the posterior fossa. Tandem gait is impaired in the early stages of cerebellar disorders and may be particularly useful in the evaluation of pre-ataxic stages of progressive ataxias. Impaired inter-joint coordination and enhanced variability of gait temporal and kinetic parameters can be grasped by wearable devices such as accelerometers. Kinect is a promising low cost technology to obtain reliable measurements and remote assessments of gait. Deep learning methods are being developed in order to help clinicians in the diagnosis and decision-making process. Locomotor adaptation is impaired in cerebellar patients. Coordinative training aims to improve the coordinative strategy and foot placements across strides, cerebellar patients benefiting from intense rehabilitation therapies. Robotic training is a promising approach to complement conventional rehabilitation and neuromodulation of the cerebellum. Wearable dynamic orthoses represent a potential aid to assist gait. The panel of experts agree that the understanding of the cerebellar contribution to gait control will lead to a better management of cerebellar ataxias in general and will likely contribute to use gait parameters as robust biomarkers of future clinical trials.

**Keywords** Cerebellum · Gait · Posture · Cerebellar ataxia · Rehabilitation · Therapies

### Introduction

A contribution of the cerebellum to the regulation of posture and gait was first been suggested two centuries ago by Luigi Rolando (1809) and Marie-Jean-Pierre Flourens (1824) on the basis of animal studies. The first description of ataxic

gait in human was reported by William Alexander Hammond (1871) describing the “drunken gait” in patients suffering from cerebellar disease [1, 2]. Tremendous progress has been made in our understanding of the mechanisms of ataxic gait thanks to studies in animals, modern neuroimaging tools and clinical research. The cerebellum has been found to play a key role within major loops connecting cerebral cortex, brain stem nuclei and spinal cord to cerebellum. Cerebellar circuitry receives sensory inputs from postural effectors including proprioceptive, exteroceptive, visual and

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vestibular feedbacks. It participates in the adaptation of the motor commands subserving gait and postural control [3, 4].

Clinical features of cerebellar ataxic gait include a widened base with increased double limb support duration, unsteadiness, irregular steps, trunk instability, difficulties with interlimb or intralimb coordination, increased variability of steps, reduced step length and speed as well as cadence and lateral veering [5–9]. Ataxic gait is clinically evaluated in the common scales rating ataxia such as SARA, ICARS or BARS. While the contribution of the cerebellum in gait and posture is increasingly understood, methods to objectively quantify these functions are not commonly applied in clinical practice. A number of proposals have been made to assess gait and posture through motion analysis. These techniques evaluate center of mass and center of pressure travelled way through stabilometric platforms, joint kinematics and kinetics either through camera-based systems or using wearable devices such as gyroscopes, accelerometers and electromyographic probes, as well as the more recent Kinect technology [6–12]. Currently, therapies aiming to compensate ataxic gait and posture are mainly based on rehabilitation programs and are yet to be fully developed.

The aim of this Consensus Paper is to gather a panel of experts to review the current knowledge on the contributions of the cerebellum in gait, to discuss the pathogenesis of ataxic gait and its assessment using recent tools, as well as actual treatments. The experts discuss also the use of gait parameters as biomarkers for future clinical trials.

## Neural Basis of Balance

This section broadly covers the neural basis of balance. We highlight converging evidence across structural and functional neuroimaging techniques and emphasize the important role that the cerebellum plays in balance. Additionally, we cover the potential for balance-training induced neuroplasticity.

Approximately 30% of the population will experience balance challenges in their lifetime [13]. These balance challenges can profoundly impact daily life and can manifest in static balance challenges such as difficulty standing in place as well as dynamic balance challenges including difficulty initiating or coordinating gait. Balance challenges often transcend clinical diagnostic groups and can arise from a variety of genetic, developmental, and environmental factors. This diversity in population samples, coupled with the diversity in structural and functional neuroimaging approaches used to investigate them, has yielded a heterogeneous literature surrounding the neural basis of balance. While it is clear that balance is a whole-brain phenomenon that does not take root in one specific

neural circuit, the structures most commonly associated with balance across populations and imaging techniques include the basal ganglia, thalamus, hippocampus, inferior parietal cortex, frontal lobe regions, and cerebellum [14, 15]. Indeed, some of these structures, such as the basal ganglia and cerebellum, are often associated with general motor behavior. However, many of these structures are more commonly associated with sensory gating, sensory integration, memory, and cognition, further demonstrating that balance involves the careful recruitment of structures throughout the brain to integrate sensory, motor, and cognitive functioning.

While balance is not exclusively cerebellum-dependent, the cerebellum may play a particularly important role in the act of balancing and coordinating movement. Across structural and functional neuroimaging investigations into the neural basis of balance, the cerebellum is the most commonly implicated brain region [14, 15] with higher gray matter volume in the cerebellum is associated with better balance in clinical and non-clinical populations [16–20]. Findings of cerebellar involvement in postural control not only converge across structural and functional imaging techniques but are supported by animal models, potentially indicating an evolutionarily conserved role of the cerebellum in balance [21]. Further, perturbations to cerebellar development or damage to cerebellar structures can lead to cerebellar ataxia, a condition characterized by poor coordination of gait and balance as well as limb and eye movement [22]. While cerebellar ataxia consistently impacts overall coordination and postural control, its diverse etiologies may explain the varied success of rehabilitation programs [23] and transcranial direct current stimulation treatments [24] geared toward improving cerebellar ataxia symptoms. These diverse etiologies may also help to explain the contributions of specific cerebellar structures to dynamic and static balance challenges [25]. Since the cerebellum is an anatomically complex region comprised of several structures that are differentially involved in planning and executing sensory, motor, and cognitive tasks, specific cerebellar structures are likely more involved in balance than others. For example, the cerebellar vermis, an early developing cerebellar structure which integrates somatosensory input from the head and proximal body parts, is frequently implicated postural control in humans and likely plays a key role in balance [26–29]. Balance has also been associated with white matter tracts such as the cerebellar peduncles, which transmit information between the cerebellum and key nuclei in the brainstem and subcortical areas. Specifically, better balance is generally associated with increased microstructural integrity (higher fractional anisotropy and/or lower mean diffusivity) of the superior and middle cerebellar peduncles but decreased

microstructural integrity of the inferior cerebellar peduncles [27, 30].

The study of balance intervention has shown the potential for balance training to induce neuroplasticity not only in the cerebellum but also across the cerebrum. In fact, only 90 min of balance training spread over the course of two weeks has been shown to induce structural change in cortical gray and white matter [31]. After this short period, balance-related neural changes occurred in brain areas involved with sensory and motor related processing such as the supramarginal gyrus and the supplementary motor area [31]. These early-developing changes to the brain underscore how influential balance training is on whole brain structure and function. However, over the extended course of balance training, more complex patterns emerge that involve positive and negative changes in gray matter volume and white matter structure over time. Generally, increased gray matter volume and decreased white matter volume and structural integrity (higher mean diffusivity and/or lower fractional anisotropy) in both the cerebellum and hippocampus are associated with balance improvements across longer time periods [30, 31]. Interestingly, robust cortical gray and white matter changes are typically most apparent during initial stages of balance training but are less detectable after extended periods of intensive intervention [31]. However, these patterns of neuroplasticity are often specific to the type of balance training used and also the population studied. Balance-training related neuroplasticity in key brain regions such as the hippocampus may also contribute to the established relationships between balance training and improved cognitive function and memory across clinical and non-clinical populations [18, 32]. The cognitive improvements following balance training coupled with our understanding of the neural basis of balance and balance-related neuroplasticity emphasize the shared neural basis of balance and cognition. Therefore, understanding the neural basis of balance may ultimately improve our understanding of brain and behavior relationships across a variety of functional domains.

## Cerebellum and Rhythms

Precise timings and patterns of muscular activation subserve healthy gait. The execution of muscular coordination is devolved to networks of interacting neurons known as central pattern generators, localized in the spinal cord [33], whose activation depends on command centres. Additional layers of regulation, based on sensory feedback and timing cues, bring the flexibility necessary to adapt movements to environmental constraints. The inner connectivity of the cerebellum early fed hypotheses about its role in sensorimotor timing. The Purkinje cells, located in the cerebellar cortex, are the sole output of the basic cerebellar circuit module.

They receive multiple inputs from granule cells that relay mossy fibers via parallel fibers, and numerous synaptic junctions from one climbing fiber [34]. Mossy fibers, which convey multiple sensory modalities to the cerebellar cortex to 50 billions granule cells, convert the sensory context into a vast set of patterns, as originally proposed by Marr [35] and Albus [36]. This distinctive anatomical feature has been hypothesized to support timing errors detection, and the study of the temporal relation between conditioned responses and associated afferences supported this conceptualization of the cerebellar function [37]. The anatomy of this circuit-level model is the substrate of the cross-modality contextualization of sensory events, and its physiology, specifically the plasticity of parallel fiber to Purkinje cell synapses [38], adds the potential of temporal relation learning [39]. The Marr-Albus-Ito model successfully accounted for the cerebellar contribution to sensorimotor coordination and learning, and paved the way for other models of the cerebellar function [40].

The comparison of online afferences and previous patterns of activation supports the role of the cerebellum in sensory discrimination during movement [41]. Such comparison represents an adaptive prediction of sensory input and qualifies the cerebellum for feed-forward computation [42–46]. The cerebellum possesses the properties of an associative memory and would temporally treat proprioceptive information to map them into motor command. The timing hypothesis proposes that the cerebellum would invoke an explicit representation of time [47]. Olivary cells are indeed characterized by rhythmic sub-threshold membrane potential oscillations whose apex potentiates spike occurrence by putting the neuron at a potential closer to the threshold [48–51]. Jacobson, Rokni, and Yarom [52] proposed, within the cerebellar cortex, an association of the contextual inputs carried by the mossy fibers with a temporal pattern. In other words, cerebellar temporal patterns would not be the byproducts of an inflexible clock, but could be generated “upon request”. Mathy et al. [53] evidenced the dependence of the number of olivary cells spikes on the phase of the subthreshold oscillation [53]. Olivary cells bursts would convey more information than an on–off state. Subthreshold oscillations, in addition to their role as a timekeeping device, would assign a level of saliency to afferences as a function of their phase, in-phase afferences being the most prone to enhance plasticity mechanisms in Purkinje cells. This mechanism could meet the premises of both timing, and classical error prediction theories.

There is now no doubt about the temporal encoding of motor-related afferences in the cerebellar granular layer but a unified model providing a compelling account for the whole sum of experimental data is still missing, the functional heterogeneity of the cerebellum having been underestimated [40]. The investigation of muscles synergies in

patients affected by cerebellar ataxia opens the possibility to clarify the contribution of the cerebellum in the spatial and temporal domains: every locomotor cycle relies on appropriate strengths and timings of muscular activation to generate torques along the kinematic chain. Comparing reaching movements in healthy participants and patients affected by cerebellar ataxia, Berger et al. [54] reported an alteration of the temporal patterning of the synergies while their spatial structure was preserved. The analysis of locomotor patterns in patients also revealed an impairment in the control of muscular activity duration [55].

## Cerebellum Gait, and Mental Imagery

The cerebellum is involved in motor preparation, execution, adaptation, learning and automation. In particular, the cerebellum plays a major role in stance, balance control and intra- and inter-limb coordination for goal-directed limb placement. All these three activities are tightly combined in locomotion. In animal, the neural network monitoring walking includes sensorimotor, parietal and visual cortices, thalamus, basal ganglia, cerebellum, subthalamic and mesencephalic (cuneiform and pedunculo-pontine nuclei) locomotion regions, reticular formation, and vestibular and red nuclei projecting to spinal cord gray matter [56]. Encephalic centers contribute to locomotor planning, initiation and adaptation based on proprioceptive, exteroceptive, visual and vestibular feed-backs, while interconnected spinal cord modules determine rhythms and pattern of current flexor/extensor activity. The cerebellum would precisely adjust and time intra- and inter-limb coordination and kinematics, such as speed. This core network well studied in quadrupedal rodents must also be present in human with possible anatomofunctional reconfiguration due to bipedal walking. Low-resolution SPECT and PET neuroimaging techniques applied after overt locomotion confirmed that the human locomotion-related network shares the main neural nodes observed

in rodents, and includes vermis and paravermis of the cerebellar anterior lobe (for instance, [57]). High-resolution functional MRI was also used to thoroughly identify the network dedicated to mental imagery (MI) of standing and walking.

## Mental Imagery of Stance

Standing imagery showed cerebellar activation in:

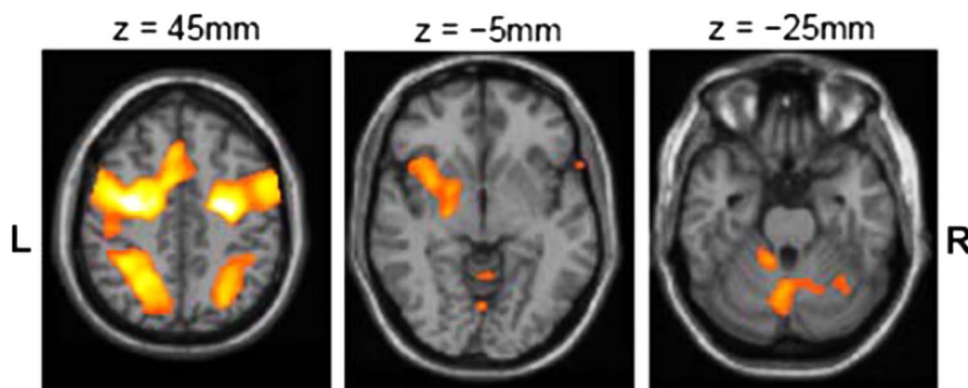
1. Vermis of lobules 4–5–6, right hemisphere of lobules 3–4–5, bilateral hemisphere of lobule 6 and right or bilateral hemisphere of lobules 6-crus1 [58] as well as vermis of lobule 9 [59].
2. Bilateral lobule 6 [60]
3. Bilateral lobule 6 including the vermis [61] (Fig. 1).

However, Jahn et al. emphasized the prominent activation of thalamic and lenticular during stance imagery. It is noteworthy that motor imagery of dynamic and complex balance tasks caused strong and bilateral activation of cerebellum (lobules 4–5 and 9) [31, 62]. Therefore, rostral vermal and motor anterior lobe activation may subservise mental simulation of axial and leg muscles tonic recruitment in stance, and balance control due to potential postural instability. Activation of lobules 6 and 7 could be in relation with executive functions (working memory, attention) depending on the intrinsically connected fronto-parietal network [63].

## Mental Imagery of Locomotion

An ALE meta-analysis of MI found that all studied movements, including gait, activated a common bilateral (pre-)fronto-parietal network mainly encompassing: prefrontal, lateral and medial premotor, anterior insular and parietal cortices, thalamus, basal ganglia and cerebellar lobule 6 [64]. Inconstant implication of the motor cortex was noted. However, activation map during MI can vary in function on the type of movements, MI modality (visual

**Fig. 1** Significant group-level cerebral activation pattern during locomotion imagery versus standing imagery. Axial slices showing the bilateral fronto-parietal cortical network (L : left), anterior insula and lenticular nucleus (middle) and anterior cerebellar lobe (R : right) associated nodes. From : Wagner et al. [61]



versus kinesthetic imagination), individual abilities (good versus bad imagers), age and experimental paradigms (for instance, the control task: rest versus lying or standing). Concerning specifically MI of gait, cerebellar activations were observed in left lobules 1–6 and right lobules 6–crus 1. MI of walking is associated with activations in vermis and hemisphere (lobules 4–5 bilaterally and right lobule 6 [58] and 2007; [60] as well as crus 1 and 2 [58] and 2007). Wagner et al. [61] found differential cerebellar activation correlated with the curvature of imagined walking path: right lobule 6 (walking along a straight line), vermis and bilateral hemisphere of lobule 6 (right curve) and left lobule 6 and right crus 1 (left curve). MI of running recruited vermis and hemispheres of lobules 3–6, right hemisphere of lobules 6–crus 1 [59], whereas imagined brisk walking recruited vermis of lobule 4 and left hemisphere of lobules 6 and 8 [65]. Of interest, Cremers et al. [65] reported correlation between walking speed and left cerebellar activation (vermis of lobule 5 and crus1/2) in conjunction with right prefrontal and inferior parietal cortices. Cerebellar clusters were larger during running imagery than during standing or walking imagery. Stronger cerebellar activation of good imagers compared to bad imagers was detected in bilateral crus 1 and 2 [66]. When compared to gait-like plantar activation, MI of gait yielded activation of left lobules 4–5–6, and, to a less extensively, of right crus 1 [67]. Contrasting MI of walking versus MI of standing recruited the left lobule 4 and the right lobule 6 [60]. Finally, no age-related changes were recorded in cerebellum during MI of gait: only executive prefrontal (BA 10–11), motor (BA 4–6 medial) and hippocampal exhibited increased activity with age [68].

In conclusion, MI of gait involves a core intrinsically connected fronto-parietal network comprising in the cerebellum:

1. Anterior lobe (kinematic simulation of gait and associated stance) in conjunction with premotor structures, whose vermis may, at least, control speed, and
2. Lobules 6 and 7, especially crus 1–2 (executive control, vividness of mental imagery, complexity of the task).

This core network would recruit in a context- and task-dependent manner specific such as premotor/motor (motoric emulation), hippocampal/cuneus (neuronavigation, space representation), specific sensory cortex and corresponding interconnected cerebellar areas.

## Tandem Gait and the Cerebellum

The terminology of tandem gait refers to a sensorimotor task during which the standing subject is asked to walk in a straight line putting one foot immediately and sequentially in front of the other [4], Figs. 2, 3). Tandem walk is

classically described in many textbooks of neurology as one of the most sensitive tests to detect signs of ataxic gait in cerebellar diseases, the task requiring the coordination of a high number of skeletal muscles [2, 4]. The procedure is considered as the most useful clinical test to unravel a cerebellar dysfunction from the motor standpoint [7]. Patients themselves often consider the task as highly challenging. The importance of this clinical procedure is also reflected by the clinical scales assessing motor phenomenology in cerebellar disorders (see below) which take into account the importance of tandem gait for the clinical quantification of motor deficits and their follow-up.

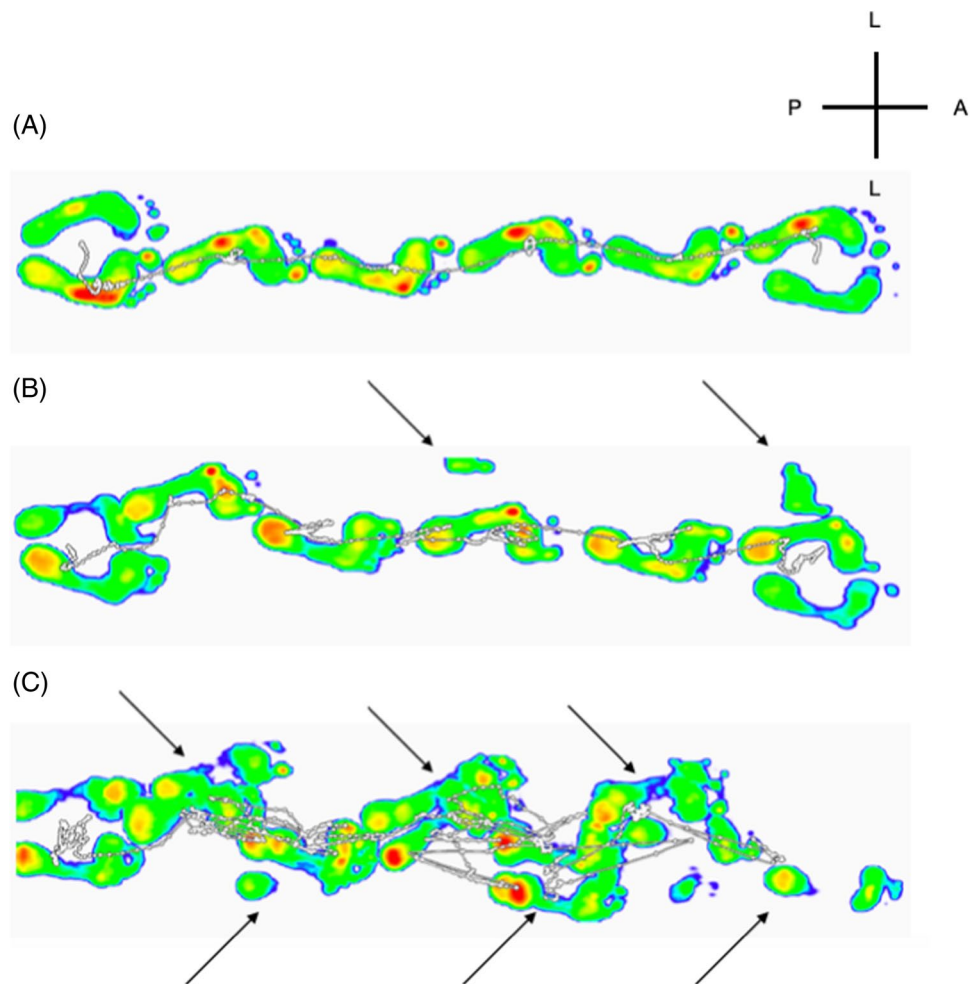
### Role of Cerebellum in Tandem Gait: Clinical Observations, Anatomical and Physiological Considerations

Sitting, stance and gait are often impaired in midline cerebellar lesions [69]. Lesions in the medial and intermediate portions of the cerebellum, in particular in the anterior lobe, impair movements related to equilibrium. Whereas lower vermal lesions are often associated with a pluridirectional increased body sway, lesions in the anterior lobe at the level of the upper vermis tend to increase the anterior–posterior oscillations at a lower amplitude [69].

Bastian et al. described in 1998 a series of 5 children who underwent a resection of posterior inferior cerebellar vermis (ranging from lobules VI–X; the posterior vermis receives inputs from peripheral somatosensory, vestibular and visual systems) and who exhibited an isolated impairment of tandem gait [70]. The authors suggested a major role of the interruption of parallel fibers running through the arborization of Purkinje neurons and crossing the midline as the main explanation of incoordination observed during tandem gait. The interruption of the linking message transported by parallel fibers would cause errors in the discharge of Purkinje neurons and subsequently abnormal firing patterns in cerebellar nuclei, resulting in an ataxic tandem walk. Notably, more recent researches have also shown a double-crossing of the cerebellar midline [71, 72].

In 2013, Ilg et al. investigated the role of focal cerebellar lesions on working memory and different gait tasks in 17 young patients with chronic focal lesions after tumor resection [73]. The authors underlined the important role of postero-lateral cerebellar hemispheres and dentate nuclei in tandem gait execution. They reported an increased step variability of tandem gait mainly in lateral cerebellar lesions, implicated in visually guided movement, and dentate nuclei lesions involved in both working memory and motor tasks based on sensorimotor inputs [73, 74]. The observations fit with the general opinion that the cerebellum regulates step and stride length, cadence and reduces variability in successive cycles [69].

**Fig. 2** Example of tandem gait realized by a patient without cerebellar ataxia (A) patient presenting hemispheric cerebellar stroke (B) and patient with spinocerebellar ataxia 6 (C). The three patients had to realize a 6 paths long tandem gait starting and finishing both feet tied to each other. The grey line stands for de movement of de center of pressure. The total travelled way were recorded for the three patients and where respectively : 1763 mm for patient A, 2475 mm for patient B and 7793 mm for patient C. While patient A made no mistake realizing the task and keep its center of pressure stabilized during the task, the cerebellar patients B and C made multiple mis-steps (showed by arrows) and were unable to keep their center of pressure stabilized. L stands for lateral, A for anterior and P for posterior



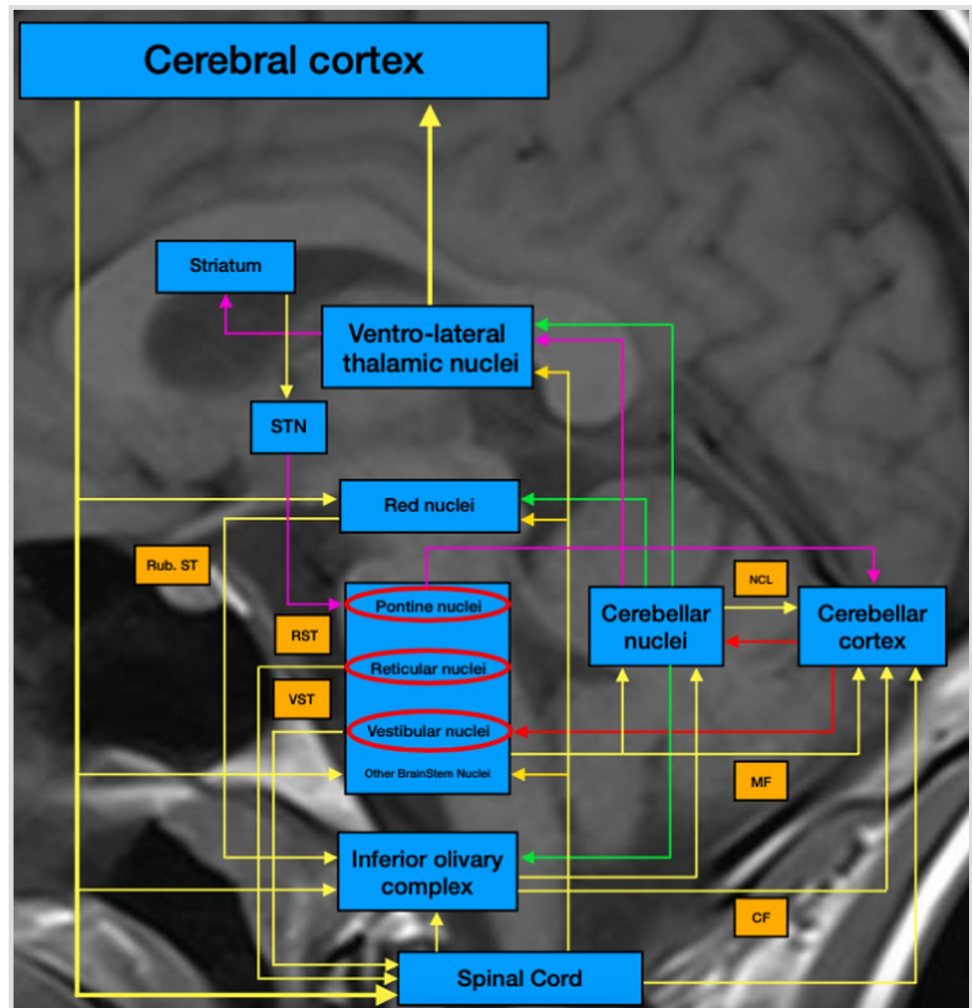
**Fig. 3** Tandem gait realized on force platform by a healthy subject



Anatomically, the cerebellum is particularly well suited to integrate postural information coming from vestibular, ocular and proprioceptive inputs [4]. The medial cerebellum modulates the activity of vestibulospinal and reticulospinal tracts, the intermediate cerebellum influences walking via projections to motor cortical areas and the lateral cerebellum contributes to voluntary modifications of the locomotor cycle [69]. Furthermore, cerebellum is a key-node within

major loops linking cerebral cortex, basal ganglia, brainstem nuclei and spinal cord. In particular, cerebellum is involved in multiple anatomical loops running in parallel and connecting the cerebellum with cerebral cortex [4, 75], Fig. 4). Cerebellar circuitry regulates dynamic balance during posture and gait. In addition, cerebellar modules contribute to the process of adaptation of sensorimotor tasks through predictive mechanisms [76]. Indeed, compelling evidence

**Fig. 4** Inspired from Grimaldi and Manto [75]. Scheme of anatomical connections of the cerebellar circuitry. Cerebellum is widely interconnected with cerebral cortex, brainstem and its nuclei, mainly reticular and vestibular ones, and spinal cord through different loops. These connections allow cerebellum to integrate many sensory inputs generated by the different postural effectors needed for the realization of tandem gait. Green arrows stand for an excitatory signal. Red arrows stand for inhibitory signal. Yellow arrows stand for simple connection signal way. Pink arrows stand for disynaptic connections between cerebellum and sub-cortical areas. RST = reticulospinal tract ; VST = vestibulospinal tract ; Rub.ST = rubro- spinal tract; CF = climbing fibers ; MF = mossy fibers ; NCL = nucleo-cortical loop ; STN = sub-thalamic nucleus



suggests that the cerebellar circuitry operates as a forward controller and contributes to the predictions inherent to sensorimotor control and adaptative behavior, resulting in movement coordination and postural tone regulation [3, 77, 78]. The prevailing theory considers that cerebellar micro-complexes compare expectations from the actual sensory feedback and generate signals to ensure an adaptation of motor behavior, as a forward internal controller [3, 76]. The comparison of sequences of sensory events with previously stored sequences allows the correction of motion patterns. Match and mismatch are employed to recalibrate the forward model, in line with the hypothesis of Molinari on sequencing processes handled by the cerebellum [79]

While these two function may not be independant, [80] cerebellum regulates timing and synergy, allowing intra- and interlimb muscles activity coordination. Anatomical, neurophysiological, behavioral, and clinical research emphasize the role of cerebellum in the modulation of timing and amplitudes of agonist and antagonist muscle contraction control. Cerebellar patients show distorted timing-related processes, explaining impairment in

different tasks requiring precise timing and synergy [81]. Additionnally, cerebellum contributes to the scaling of anticipatory postural responses during postural perturbations and participates in the adaptation of postural responses based on prior experience through cerebello-cerebral loops tuning the magnitude of long-latency transcortical reflexes [82, 83].

### Assessing Tandem Gait: the Need for a Consensus

Tandem gait accentuates all features of ataxic gait, including postural and balance control, timing and motor adaptation of successive steps. Tandem gait or stance analysis are indeed items of clinical scales evaluating cerebellar ataxic patients such as International Cooperative Ataxia Rating Scale (ICARS) [84], Brief Ataxia Rating Scale (BARS) [85] or Assessment and Rating of Ataxia (SARA) scale [23]. Tandem gait assessment is particularly relevant for early stages of cerebellar diseases as shown for preclinical spinocerebellar syndrome [86], Luis [87] or minor cerebellar motor syndromes (Table 1).

**Table 1** Scales evaluating mainly the cerebellar motor syndrome. BARS and ICARS only describe an inability to walk in tandem position to score gait impairment in cerebellar patients, while SARA differentiates stage 1 and 2 on the basis of the ability to perform 10 consecutive steps in tandem position

Scales	Selected references	Category	Quotation	Tandem gait evaluation
ICARS	[84]	Postural and gait disturbances, walking capacities	0 to 8	Gait almost normal naturally, but unable to walk with feet in tandem position (0–1)
BARS	[85]	Postural and gait disturbances, walking capacities	0 to 8	Gait almost normal naturally, but unable to walk with feet in tandem position (0–1)
SARA	[23]	Gait	0 to 8	1. Slight difficulties, only visible when walking 10 consecutive steps in tandem 2. Clearly abnormal, tandem walking > 10 steps not possible

There is currently no consensus on the best procedure to evaluate tandem gait. The clinical protocols vary on number of steps required per trial, numbers of trials allowed, training before execution, use of actual or imaginary lines, the use of vision (eyes open or closed) and instructions on the position of arms and body posture [2]. While some authors record number of missteps [88], others evaluate « Stride», « Stance» and « Swing» time, corresponding to each phase of tandem gait [70]. Therefore, there is an urgent need to define and validate a universal procedure of tandem gait assessment. Videos and smartphone applications represent opportunities for such an endeavour, since many research groups or clinicians may not get an easy access to complex or expensive equipment assessing gait.

## Vestibulo-Cerebellar Interactions

### Anatomical and Physiological Connections Between the Vestibular Nuclei and the Cerebellum and Their Pathophysiology

Physiologically, pathophysiologically, and clinically, the interaction between the vestibular and cerebellar systems is of high relevance. Phylogenetically, there is even evidence that the cerebellum arises from the vestibular system (Straka, personal communication, [89] which strongly underlines this interaction.

The vestibular nuclei project to the ocular motor nuclei (vestibulo-ocular reflex (VOR)), the spinal cord (vestibulo-spinal reflex (VSR)), the thalamus, the cerebral cortex and to cerebellar areas, in particular the flocculus/paraflocculus, nodulus and uvula. On the other hand, there are intense cerebello-vestibular connections from the flocculus/paraflocculus, nodulus and fastigial nucleus [90]. These broad and often reciprocal interactions indicate the importance for physiological function and dysfunction in both vestibular and cerebellar disorders (Fig. 5).

## Vestibular Projections to the Cerebellum

### Primary Vestibulocerebellar Projections

Primary vestibular afferents target neurons in the ipsilateral superior (SVN), medial (MVN), descending (DVN), and ventral lateral vestibular nucleus (LVNv) – not dorsal (LVNd), and ventral Y-group (Yv) [91]. Primary vestibular afferents further project directly to the ipsilateral nodulus (semicircular canals) and ventral uvula (otolith) in the caudal vermis [92, 93], and lobules I and II in the anterior vermis [91, 94], but not to the flocculus/ventral paraflocculus.

### Secondary Vestibulocerebellar Projections

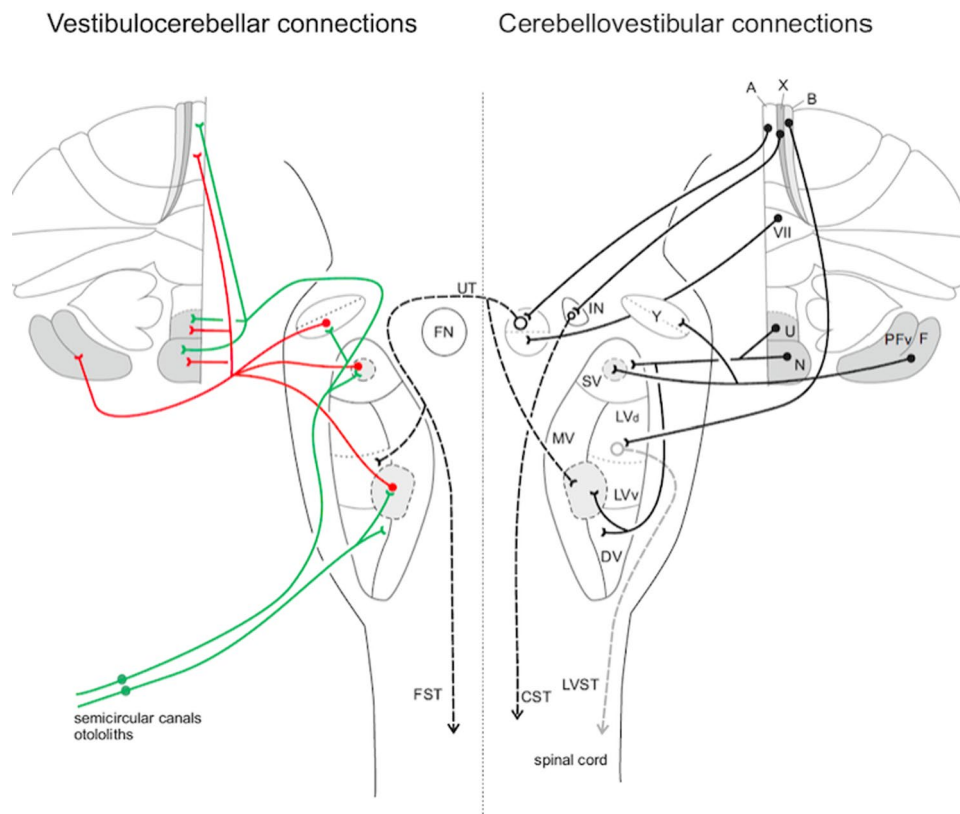
All vestibular nuclei receiving primary vestibular input, including Yv (not LVNd), project bilaterally—in part by cholinergic neurons—to the same cerebellar regions that are targeted by primary vestibular afferents [91, 95]. In addition, these vestibular nuclei (central SVN, MVN, DVN, Yv) project bilaterally to the flocculus and ventral paraflocculus [94].

## Cerebellar Projections to the Vestibular System

Purkinje cells of the flocculus, nodulus, uvula and anterior vermis, as the fastigial nucleus (FN) project to vestibular nuclei: Purkinje cells in the flocculus/ventral paraflocculus (PFv) (zone F1, F3) project to horizontal canal neurons in the magnocellular MVNm, Purkinje cells in the flocculus/PFv (zone F2, F4 – not in monkey) project to anterior canal relay neurons in central SVN and Yd. The uvula and nodulus target neurons in peripheral (non-secondary) SVN and areas in the caudal MVN and DVN that mainly project to the cerebellum and spinal cord [90, 91].

Anterior vermis. Purkinje cells of the lateral B-zone in the anterior vermis provide a strong projection to LVNd [96], which (together with DVN) gives rise to the lateral vestibulospinal tract (LVST) projecting to spinal cord segments





**Fig. 5** Summary diagram of connections between the vestibular system and the cerebellum. The connections on the left side demonstrate vestibular inputs to the cerebellum including primary vestibular afferents from the semicircular canals and otoliths (green). Efferents from vestibular nuclei are indicated in red. The connections arising from the cerebellum to vestibular nuclei are shown on the right side with solid black lines. The dashed lines indicate pathways arising from deep cerebellar nuclei. The shaded areas in the cerebellar cortex correspond to the vestibulocerebellum. The encircled areas within the vestibular nuclei indicate the location of second-order neurons with

controlling forelimb and hindlimb muscles [97, 98]. Purkinje cells of the vermal X-zone target interstitial neurons in the cerebellar white matter with which give rise to direct cerebellospinal projections [90, 91, 99], and the medial A-zone of the anterior vermis projects to rostral fastigial nucleus (FNr) and MVNmc, those of lobule VII project to the caudal FN (FNc) [100].

**Fastigial nucleus.** FNr and FNc project both bilaterally to LVNv, MVN, DVN (plus reticular formation and spinal cord) via the crossing uncinate tract (UT) and ipsilateral fastigiobulbar tract [101]. Fastigiobulbar projections down to cervical level as vestibular projections arise predominantly from FNr, reticular projections mostly from FNc [90, 102].

### Physiology and Pathophysiology

As mentioned above the key cerebellar structures interconnected with the vestibular system are the flocculus/paraflocculus

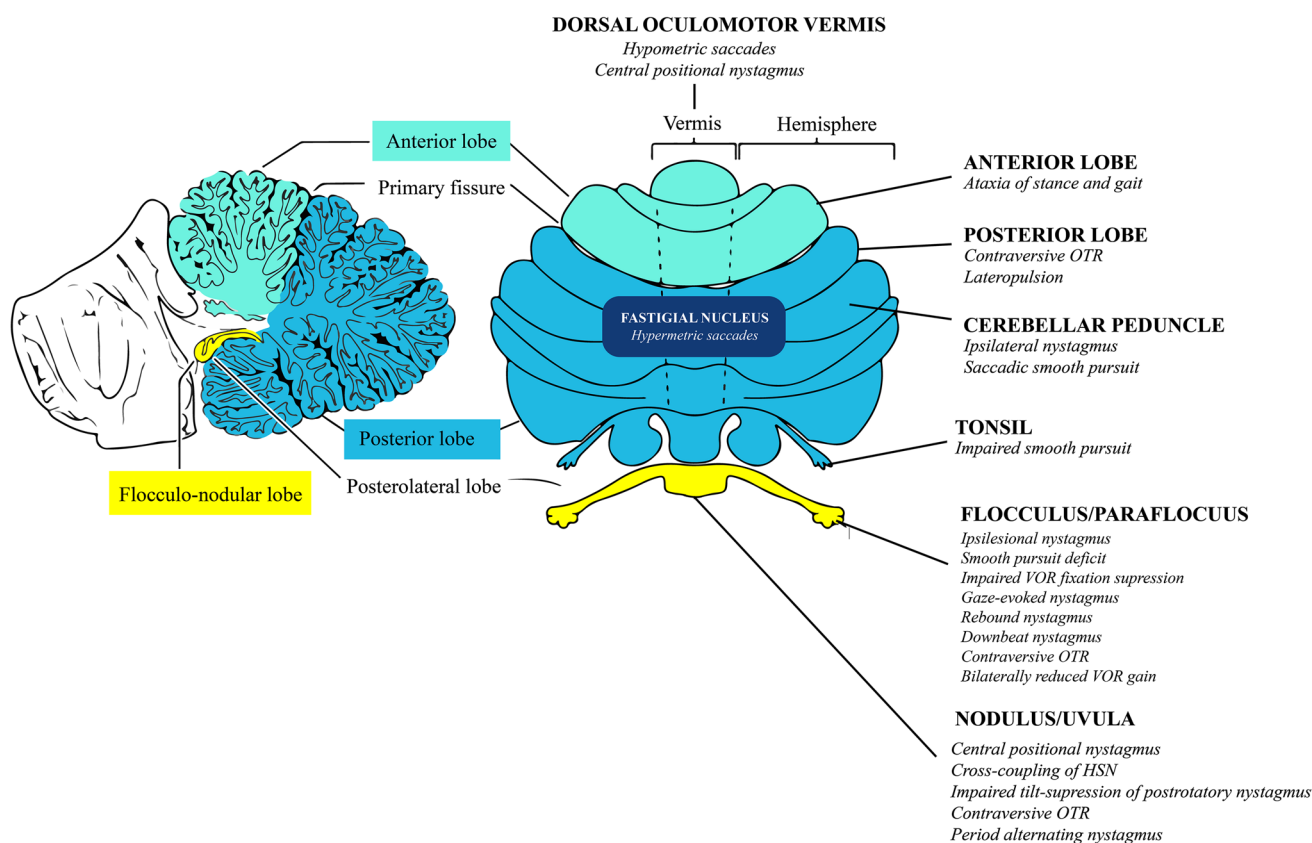
and posterior vermis (the vestibulo-cerebellum) including the FN nucleus [103]. Physiologically, the flocculus/paraflocculus are relevant for:

and posterior vermis (the vestibulo-cerebellum) including the FN nucleus [103].

Physiologically, the flocculus/paraflocculus are relevant for:

- Oculomotor function, namely smooth pursuit, gaze-holding function as part of the neural integrator with the nucleus praepositus hypoglossus for horizontal and the interstitial nucleus of Cajal for vertical gaze-holding, as well as optokinetic nystagmus
- Vestibular function, for instance, VOR adaptation or suppression during combined head and target movements.

The FN and posterior vermis are relevant for balance and postural control, namely estimation of motion and spatial orientation, via vestibular and efference-copy signals and by combining signals from the semicircular canals and otolith organs. This system is highly adaptable, leading



**Fig. 6** Overview of the relevant anatomical structures of the cerebellum for the interaction between the vestibular and ocular motor system and typical clinical signs (from Strupp et al. [104])

to learning processes and adaptation after peripheral and central vestibular lesions.

Pathophysiologically, the cerebello-vestibular interaction is highly relevant: in Fig. 6, the different vestibular and ocular motor signs due to cerebellar dysfunction are summarized. Therefore, clinical lesions of the flocculus and posterior vermis can manifest with dysfunction of the VOR and VSR, leading to dizziness and postural imbalance as well as impaired spatial orientation.

### **Vestibular Syndromes Due to Impaired Cerebellar Function and Vice Versa (Fig. 6)**

Examples of directly impaired vestibular function due to primary cerebellar dysfunction are unilaterally or bilaterally reduced VOR due to lesions of the flocculus/paraflocculus, as demonstrated in animal studies [105, 106] as well as in patients with structural lesions [107] and cerebellar ataxia of various aetiologies [108]. On the other hand, a hyperactive VOR was also found in patients with impaired cerebellar function due to disinhibition [109]. Impaired VOR suppression due to floccular lesions [110] as well as abolished VOR tilt suppression due to uvulo-nodular lesions [111, 112] are other examples.

There are many disorders with a combined impairment of vestibular and cerebellar function, such as Cerebellar Ataxia, Neuropathy and Vestibular Areflexia Syndrome [113]. The clinical implications of these examples are that patients with cerebellar disorders need a careful examination of the vestibular system and patients with vertigo and dizziness require a systematic examination for cerebellar signs. “Cerebellar dizziness”—accompanied by typical cerebellar ocular motor signs such as downbeat nystagmus or impaired VOR suppression—is a clinically highly relevant entity [114] which also clearly shows the interaction between both systems, however, it is still often overlooked.

## **Accelerometers and Gait Ataxia**

### **Basis of Accelerometry**

Accelerometers detect body motion-induced accelerations. The basis of the measurements is explained by a mass-spring system [115–118]: a mass is displaced when acceleration is applied, generating a force in a spring connected to the mass. Thus, acceleration can be calculated by a combination of Newton’s second law and Hooke’s law [118]:  $a = F / m = kx$

/ m; where a: accelerometer (m/s<sup>2</sup>), F: force (N), m: mass (kg), k: spring constant (N/m), x: displacement (m).

Several accelerometers are based on methods of signal transduction, including piezoresistive, piezoelectric, and differential capacitive accelerometers [2, 115–117]. Piezoelectric types are only sensitive to dynamic accelerations, while piezoresistive and capacitive accelerometers can respond to both dynamic and static accelerations (e.g. gravity). Thus, the latter type can capture posture-related activities (sitting, standing, lying, walking, or falls) [117].

Accelerometers have been employed to estimate physical activities, defined as “any bodily movement produced by skeletal muscles that require energy expenditure” [119], under free-living conditions. For the measurement of basic human activities, accelerometers must cover an amplitude range of -12 to 12 g and a frequency range of 0 to 20 Hz [115]. Examples of commercially available accelerometers include the ActiGraph (ActiGraph LLC) and StepWatch<sup>TM</sup> (Modus health LLC) [120].

Accelerometers have also been applied for gait analysis [121, 122]. Identification of the subject’s foot-strike events enables computation of gait parameters including the number of steps, step interval (or cadence), gait variability, and asymmetry [11]. Various algorithms, such as template-matching, Pan–Tompkins, Dual-axial, and Wolf methods, allow the extraction of gait strike-induced accelerations from all motion-induced signals obtained with a single waist-mounted accelerometer [123, 124]. The walking speed, step length, and walking distance can also be computed when the location of the walking subject can be tracked correctly.

### Accurate Gait Characterization by Long-Term Recording

Following the finding that free-living gait is characterized by lower cadence and higher variability when compared with laboratory-assessed gait [125, 126], it became clear that laboratory gait studies measure the subject’s optimal conditions rather than ordinary conditions in daily living [125]. Importantly, gait analysis during short distance walking in the laboratory is easily influenced by emotional stress caused by increased attention [127]. Furthermore, prolonged measurements on free walking have elucidated the importance of long periods of continuous walking, termed “bouts”, in gait analysis. In fact, one study showed that the characteristic gait pattern can only be obtained from analysis of prolonged bouts, more than 10 s ([126]. In another study in which bouts of durations of  $\geq 1$  min were extracted from 3-day accelerometer data, various gait parameters were measured from the sum of these extracted bouts [128, 129]. The authors concluded that specific features of individual gait disorders can only be accurately assessed by long-term monitoring of free walking using wearable accelerometers [128, 129].

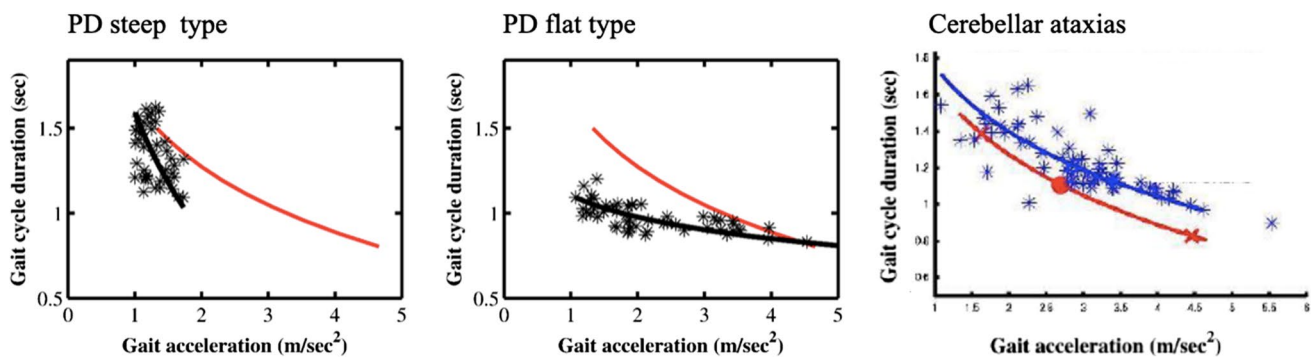
Long-term recording using accelerometers has identified ataxic gait features, including impaired inter-joint coordination and marked variability of gait temporal and kinetic parameters [130]. Thus, the accelerometer can be helpful in assessing the degree of disability in ataxic gait.

### Application in Pathophysiological Studies

Unattended long-term monitoring using accelerometers has been applied in several studies to examine changes in stepping timing and scaling of forces under various physiological and pathophysiological conditions. Such studies have documented various combinations of gait cycle duration and gait acceleration amplitude [131] where gait acceleration is defined as the acceleration in trunk movements caused by step-in and kick-off. Figure 7 shows the relationship between these two parameters, where the average value for every 10-min record was computed and plotted in two representative patients with Parkinson’s disease (PD) (Figure A and B) and in one representative patient with degenerative cerebellar ataxia (CA) (Figure C) Notably, the regression line can be determined from such plots (gait cycle duration-gait acceleration curve) [131, 133], which show that the two parameters, gait rhythm and gait force, are not selected freely and independently, but rather determined with a particular relation, characteristic for the subject. Walking with a slow cycle is associated with low amplitude of gait accelerations, while walking with fast cycle is associated with high amplitude. Notably, during these changes in free walking, both parameters always fall on the regression line. Thick red regression lines in Fig. 7A–C were obtained from 17 normal subjects. The slope of the linear regression line (thick red lines in Fig. 7A–C) for normal control subjects was  $1.20 \pm 0.29$  [132].

The range value around the regression line is narrow in patients with Parkinson’s disease (PD) [132]. A narrow range of acceleration is associated with a steep slope of the regression line (Fig. 7A), whereas a narrow range of gait cycle duration is associated with a flat slope of the regression line (Fig. 7B). These changes suggest that PD patients cannot dynamically vary the rhythm and force in daily walking and that the relationship between rhythm and force is impaired in PD. Consistent with these data, it was reported that the maximum activity that can be generated in a muscle burst is low in PD patients [134] and that PD patients can only execute movements of different amplitudes at a single, slow velocity without dynamic changes of the movement velocity [135].

In contrast, the regression line in patients with degenerative cerebellar ataxia (CA) is not significantly different from that of control normal subjects (Fig. 7C), suggesting adequate preservation of the relationship between rhythm and force in stepping despite the apparent irregular



**Fig. 7** Examples of gait cycle duration-gait acceleration relationship. Both parameters were recorded continuously for more than 24h and averaged every 10min. Data of a representative patient with Parkinson's disease (PD) (A, B) and data of a representative patient with cerebellar ataxia (C). Gait acceleration is defined as the acceleration in trunk movements caused by step-in and kick-off. Black thick line in

(A, B) and Blue thick line in (C): corresponding regression line. Red thin line in (A-C): regression line obtained from the summed average of 17 normal control subjects. The regression line of the PD patient is steep in (A) and flat in (B). The regression line of the patient with cerebellar ataxia is unchanged. See a reference of Suzuki et al. [132] for details

and in-coordinated stepping. However, the regression line in these patients is shifted upward on the gait cycle axis, reflecting compensatory reactions for the significant instability, based on the prolonged double support periods and gait cycle duration.

The above findings favor the notion that the timing processing for stepping is not specialized for a particular region uniquely capable of representing temporal information, and that the temporal controls segregate in different regions [136]. It is possible that rhythm, which is linked to the amplitudes of gait propelling forces, is controlled by the basal ganglia, whereas regular recurrence is adjusted and sustained by the cerebellum [137].

In conclusion, long-term gait monitoring using wearable accelerometers can identify disease-specific gait disorders. Furthermore, the gait cycle duration-gait acceleration curve obtained during free walking suggests a segregated control of the stepping rhythm by the basal ganglia and the cerebellum.

## Kinect and Gait Ataxia

Advancements in therapeutic perspectives of ataxia make urgent the need for novel and objective outcome measures, able to track, with the due accuracy, changes in motor functions either in interventional or observational frames.

Gait analysis provides a number of quantitative variables, which may allow the continue monitoring of patients during the entire disease course, from the early, pre-clinical phases to the overt stages, raising as a valuable biomarkers' source [86, 138, 139].

Currently, conventional gait analysis is performed only in few specialized centers, by complex and expensive systems relying on marker-based motion tracking techniques, which

definitively could affect fluidity and spontaneity of natural gait.

Depth camera technology, which is the Microsoft Kinect, may potentially outdo the main limitations of these systems, providing a cheap, portable, easy-to-operate, marker-less motion capture system, based on specific imaging characteristics and algorithms.

The Kinect system is a low-cost technology, developed for entertainment, whose features may also allow the assessment of human motor functions, even at home or into ambulatory contexts.

It is a motion-sensing input device commercialized by Microsoft Windows that with the color and IR cameras, provides depth images, and skeleton information for every tracked person estimating 25 "virtual" joints from the human shape at a frequency of 30 Hz. Hence, it allows a coherent extraction of skeleton-like structure from the depth frames, connecting a set of joints by rigid segments in time [140]. Its ease of use, no markers or sensors are needed to wear, and its accuracy in depth measurement allow the use of such technology for assessing gait with a single device [55, 141, 142].

Several studies addressed the use of Kinect to assess gait and postural control in different physiological and pathological conditions [143–146]. Indeed, it permits an accurate and reliable measurement of spatiotemporal gait parameters, whereas it lacks validity for kinematic parameters, as reported in [10].

However, it has been suggested, while processing Kinect data, to keep attention in the definition of gait events, in particular the heel strike event that defines the beginning of the gait cycle [147]. Indeed, it is often necessary to consider some methodological precautions [148]. In addition, strong signal processing or application of sophisticated algorithms, such as artificial intelligence, is recommended.

The largest body of evidence on clinical application of Kinect for gait analysis comes from studies on healthy controls or patients with Parkinson's disease, cerebral palsy, and stroke. Very few studies instead exist on ataxia, the most focusing on exergames for rehabilitation rather than on gait assessment.

However, a recent pilot study evaluated Kinect technology acceptance in a small group of ataxic children, highlighting its feasibility, tolerability and ease-of-use, and supporting the potential applicability in clinical practice, even for remote use in non-hospital settings [149].

Regarding the reliability of Kinect-based gait assessment in ataxia, Honda and colleagues [145] found that measurement accuracy of the 3d joints positions for slower movements was  $<2$  mm. In addition, they identified six 3d joints positions in natural and tandem walking able to outline the ataxic gait phenotype without resorting to sophisticated analysis algorithms, but simply observing the distribution on the anatomical planes of the joints [145].

Summa et al. then tested validity of spatiotemporal parameters acquired with the Kinect compared to those obtained with a standard motion capture system and used Kinect-based measures to classify patients depending on the aetiology or the severity of ataxia [148].

In both these studies, the marked variability, the decreased step length, the lower gait speed, and the larger step width resulted as common characteristics of ataxic gait [55, 86], although the small sample size prevents generalization of findings. However, the promising results encouraged the authors to use Kinect to digitalize the SARA.

Indeed Kinect theoretically joins the reliability of measurements, the accessibility to technology (in terms of costs and use on large scale), and the possibility of remote assessment, which are critical to develop a set of objective outcome measures for motor function in ataxia. However, confirmatory studies are still needed.

## sEMG Assessment of Gait Ataxia

Although the kinematic characteristics of ataxic gait has been extensively detailed [5, 150] only few studies presented a sEMG assessment of gait ataxia.

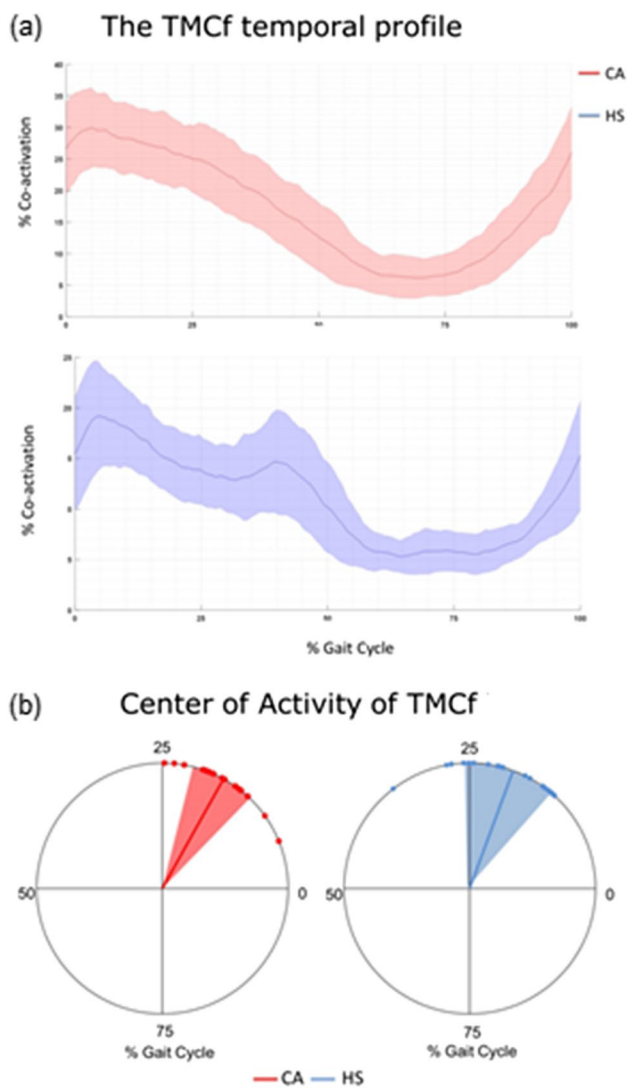
An early study from Mitoma et al. [12] revealed a common sEMG pattern in ataxic gait characterized by an excessive activity of lower limb muscles. Particularly, the activation of the distal muscles, especially the gastrocnemius muscle, was abnormally prolonged over the period they were not recruited in normal walking. Earhart and Bastian [151] revealed that muscle offsets were delayed in level walking as well as in walking with inclinations. Furthermore, although not statistically significant, they found a trend of prolonged activity in anterior tibialis muscles related to a variable shift of peak ankle dorsiflexion.

More recent studies [55, 152–154] confirmed the presence of an abnormal activation of lower limb muscles resulting in increased peak and magnitude values as evaluated by the full-width half maximum in all the investigated lower limb muscles. In general, the amplitude of muscle activity over the gait cycle was about twice that of healthy subjects [55]. The timing in muscular activations was also impaired because of the delayed peak events and the shift of center of activity in both agonist and antagonist muscles [153] (Figs. 8 and 9).

The above-mentioned sEMG abnormalities found in the lower limb's muscles resemble those found in early studies on arm muscles [80]. During fast goal-directed arm flexion movements the agonist muscles showed a delayed and prolonged initial sEMG burst [156, 157], the antagonist muscles showed a delayed activation as well [158]. These abnormalities reflected the impairment of the normal agonist–antagonist alternating activity during goal-directed fast movements, resulting in the typically slow and inaccurate movement accompanied by excessive corrections, characterizing the dysmetria of patients with ataxia [80]. Similarly, the spatial and temporal sEMG abnormalities found in the lower limb muscles during walking seem to lead to irregular limb movements with inaccurate foot position [154], abnormal transient at heel strike [154], gait variability [153], knee and ankle joint kinematics [152, 153] and abnormal production of force of pushing off during single support [12].

Martino et al. [154] suggested that especially the widening of the EMG burst, disclosed in all the investigated muscles during walking (Fig. 8), may be the expression of an inappropriate activation timing/duration directly linked to the cerebellum degeneration, as suggested by the positive correlation with the severity of pathology. Remarkably, similar wider sEMG bursts have been found in infants [159, 160], whose gait characteristics, e.g. trunk oscillations, wide step and swinging arms, high inter-stride variability, and irregular foot trajectories and intersegmental coordination [159, 160], typically resemble those of ataxic patients. The maturation of gait, which parallels the cerebellum development completion, is accompanied by a shorter muscle activation leading to a more selective and flexible control of muscles [159, 160].

Another common sEMG abnormality found in patients with ataxia is the coactivation of the antagonist muscles around the lower limb joints [152–154]. Particularly, the knee and ankle joint antagonist muscles show a high level of coactivation in all gait subphases which correlates with disease's severity and the number of falls per year [153]. Increased antagonist muscles activation may represent an additional factor that contributes to the inefficiency of walking by increasing the physiological and metabolic cost, reducing the joints power and increasing compressive and shear forces across the joint [161]. The most plausible



**Fig. 8** **a.** Time-varying multi-muscle coactivation function (TMCf) mean curves in patients with ataxia and in healthy subjects (average value in solid line and standard deviation [SD] in light color) (data from Fiori et al. [155]). **b.** Center of activity (CoA) of the TMCf: each dot in the circumference represents an individual subject's mean CoA value, whereas the mean value and SD of the CoA of all subjects are represented by the solid line and the width of the circular sector (in light color), respectively (data from Fiori et al. [155])

explanation is that patients with ataxia increase the antagonist muscles coactivation to stabilize each single joint to compensate for muscle hypotonia, irregular trajectories and unbalance. When patients with cerebellar ataxia are asked to reduce their base of support, the knee and ankle antagonist muscles coactivation markedly increases [152].

A very recent evidence [155] has also documented a widespread simultaneous activation of many muscles of the lower limb (Fig. 9), therefore irrespective of the agonist–antagonist interaction at a single joint level, suggesting a higher hierarchical control of leg stiffness during locomotion. Such a

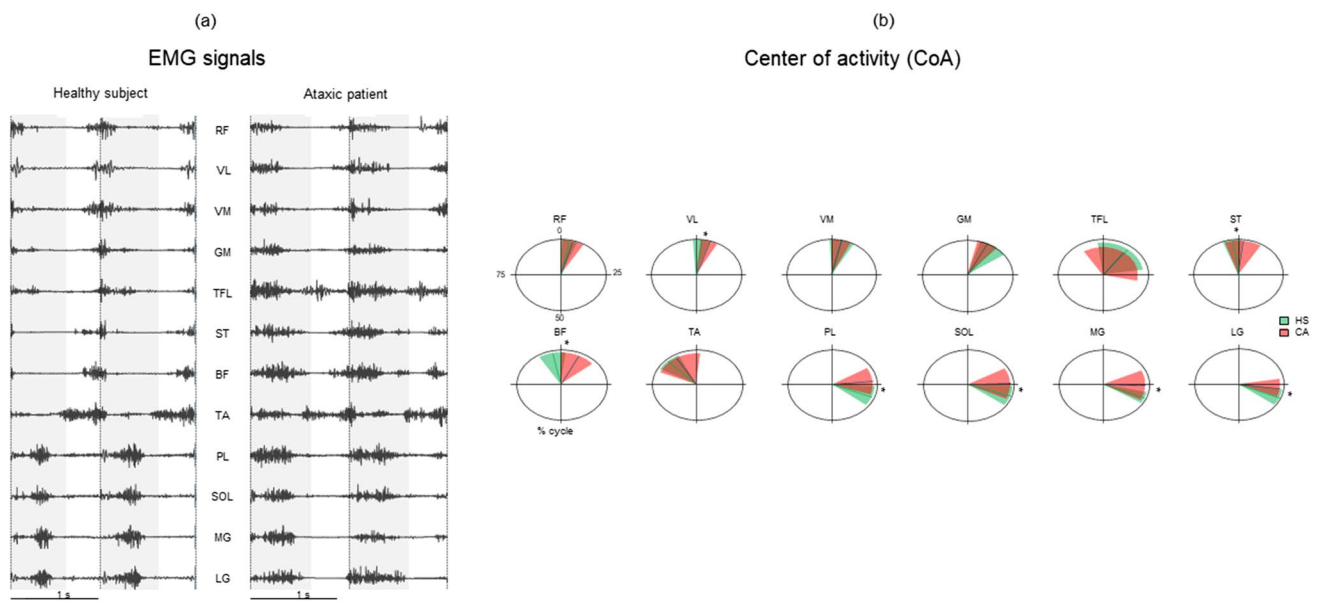
whole-limb muscle coactivation is mainly achieved during the loading response subphase, which represents the most challenging biomechanical condition, when the body weight is shifted from one limb to another and a response to the perturbation induced by the GRF is needed. Indeed, the increased coactivation is strictly correlated to the center of mass (CoM) lateral displacement and SARA score [155], suggesting that it reflects a global compensatory mechanism achieved by the CNS as gross strategy to stiffen the whole limb, purposed to minimize the CoM oscillations. In this view, the widening of the EMG burst [154], which was also found in healthy subjects walking on a slippery surface or on a beam [154], could reflect the nervous system strategy of prolonging the duration of basic muscle activity patterns to increase leg stiffness and to cope with unstable conditions or pathology [154].

In essence, the sEMG abnormalities of ataxic gait seem to witness both the primary deficits, i.e. prolonged and shifted muscle activations (Fig. 8) related to the compensatory mechanisms, i.e. increased single-joint and whole-limb muscle coactivation, to stabilize joint movements and to cope with the enlarged lateral body sway.

## Deep Learning

Deep learning has been widely applied in many research fields in this decade. In the field of medical research, deep learning combined with digital image processing has continuously obtained exciting findings in clinical diagnosis such as image recognition, and has gradually been applied in clinical practice. Gait analysis has got more and more attention in recent years of research [162–167]. With the continuous accumulation of gait clinical data, deep learning algorithms will also play an important role in the analysis and processing of gait data. Gait data is generally classified into image-based gait data and sensor-based gait data according to the data source, which is applied in fields such as person authentication, medical health, and physical fitness [122, 168]. The general methods and research progress of deep learning modeling of gait features and the application in clinical diagnosis is a typical example and a promising field for the intersection of medicine and engineering.

Gait is the movement of the lower limbs controlled by brain. Neurological diseases are often associated with gait disturbances, which has attracted more researchers' attention. In neurodegenerative diseases, the clinical symptoms of Parkinson's disease, Alzheimer's disease, mild cognitive dysfunction, and cerebellar ataxia are all manifested by gait disturbances. Therefore, we hope to find the relationship between gait changes and the progression or treatment of these diseases. Each neurological disease has its corresponding abnormal gait characteristics. Therefore, in the diagnosis of the disease, we need to manually select the most specific gait characteristics at first. For example, cerebellar ataxia has a



**Fig. 9 a.** Electromyographic row signals showing the widening of the EMG burst duration in the lower limb muscles in a representative ataxic patient compared to a healthy control (data from Martino et al. [55]). **b.** Center of activity (CoA) of the lower limb muscles activa-

tion in ataxic patients (red color) and controls (green color). The vector is the mean resultant vector of the subject's peak events expressed as a percentage of the normalised gait cycle (data from Martino et al. [55])

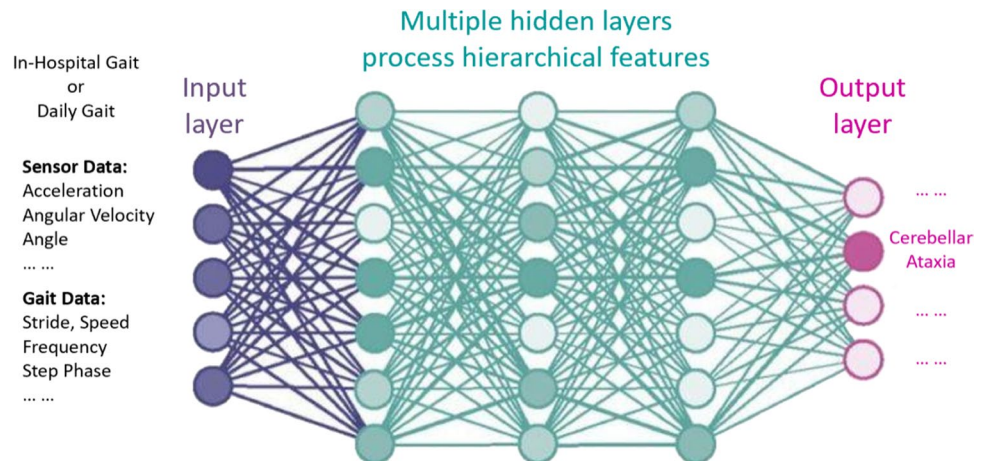
very special gait characteristic. The study of cerebellar ataxia gait has got more and more attention [163]. However, subjective feature selection has many shortcomings. We will lose a lot of useful gait information due to lack of experience. The advantage of deep learning is that it can realize unsupervised feature selection and select effective gait feature information to the greatest extent. Establishing a model between gait and disease progression through deep learning can provide a non-invasive and more efficient new method for clinical diagnosis.

Deep learning requires a larger amount of data than traditional small-sample machine learning algorithms. Therefore, we are more interested in the patient's daily gait data to make a specific clinical diagnosis based on

gait features. Daily gait is more continuous and natural, including performance in various complex environments. The limitation is that daily gait can only be collected by smart wearable devices, not by cameras. This puts forward higher prerequisites for sensor-based gait data analysis methods. Figure 10 shows the workflow of using deep learning methods for gait features to make specific clinical disease-assisted diagnosis decisions.

With the continuous accumulation of clinical single specific disease gait data, quantitative auxiliary diagnosis models based on deep learning methods will become more and more universal, and gait will be used as an essential tool of clinical diagnosis decision for neurological diseases.

**Fig. 10** Workflow of deep learning methods for gait features to make specific clinical disease-assisted diagnosis decisions



## Gait in Degenerative Ataxias

In degenerative cerebellar ataxias (DCA), neuronal loss in the cerebellum or its afferent pathways is caused by genetic factors with autosomal dominant inheritance as in the spinocerebellar ataxias (SCA) [169] or a recessive trait like in Friedreich's ataxia (FA) [170].

Gait disturbances often present as the first signs of DCA [150, 171] and are one of the most disabling features throughout the disease course. Therefore, it represents an attractive target for treatments like motor rehabilitation or therapeutic intervention.

While manifold targeted molecular treatments for inherited forms of DCAs are now on the horizon [172, 173] clinical and regulatory acceptance will depend on their proven effects on subject's ataxia using quantitative ataxia biomarkers [172]. Thus, biomarkers with high relevance for patients' daily life and with high sensitivity for individual changes are highly warranted.

### Spatio-temporal Movement Characteristic of Ataxic Gait

Symptomatically, ataxic gait is in general characterized by an increased step width, variable foot placement, irregular foot trajectories and a resulting instable stumbling walking path with high movement variability [174, 175] and a high risk of falling [176]. The characteristic high variability of walking patterns are most likely due to the complex interaction between cerebellar-induced deficits in balance control and multi-joint coordination, used safety strategies and inaccurate adjustments to appearing losses of balance [177].

Consistently, the most distinctive features of ataxic gait seem to be the high variability in several spatiotemporal gait features (e.g. variability in stride length, step width and gait cycle time, foot angles at toe-off and stance phase) [87, 175, 177–179], for current reviews see Milne et al. [180] and Buckley et al. [5]. Measures of spatiotemporal variability allowed to characterize the specificities of ataxic gait with high sensitivity to disease severity [175, 177, 181, 182] and have been shown to quantify treatment-induced improvements [183, 184]. In contrast to variability measures, quantification of average velocity, stride length or step width [175, 177, 178] seems more likely to describe cerebellar-unspecific compensatory strategies that come into play at later stages of the disease [5, 73].

### Sensitivity to Preataxic Stages of DCA

The most promising time window for the disease-modifying drugs on the horizon for DCAs are very early stages, before substantial irreversible neurodegeneration has occurred [185, 186]. Effectiveness of future intervention studies in

ataxias will depend on the availability of measures which are able to sensitively quantify progression and intervention benefits in this pre-ataxic stage (SARA score < 3) [187], when clinical signs of ataxia are still absent and clinical ataxia scores like the SARA show limited resolution [188].

In this preataxic stage, studies on straight walking delivered heterogeneous results in distinguishing healthy controls and preataxic mutation carriers. While some studies reported changes in straight walking [87, 139] other studies did not [86, 181]. This discrepancy could be explained with a variability early clinical gait signs in these populations [87, 139] in comparison to none preataxic mutation carriers show any clinical gait sign (SARA posture & gait subscore = 0) in Ilg et al. [86].

In contrast to straight walking, more complex gait conditions like tandem gait seems to better distinguish between healthy controls and preataxic mutation carriers of SCA [86, 87] with higher effect sizes and a correlation to genetically estimated duration to disease onset [86]. Furthermore, multivariate regression analysis categorized preataxic mutation carriers on a single-subject level with 100% accuracy within a range of 10 years to estimated onset. Movement features in stance and gait correlated significantly with genetically estimated time to onset [189] (Fig. 12), indicating a gradual increase of motor changes with increasing proximity to disease manifestation.

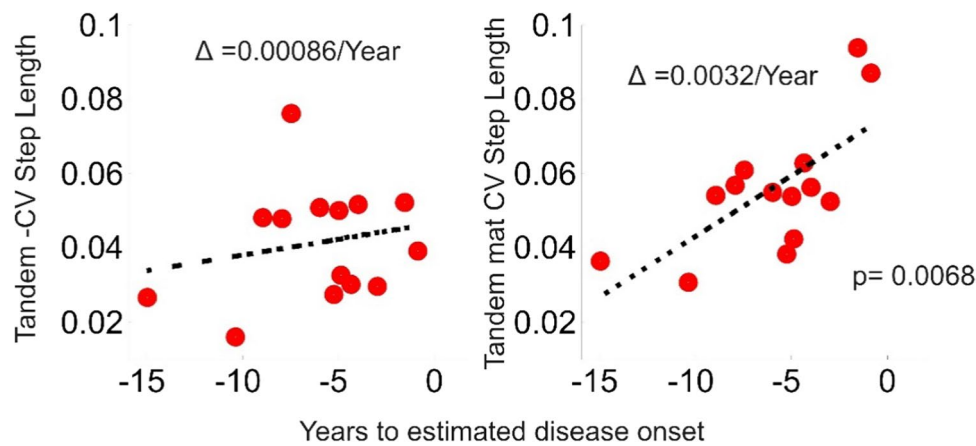
### Real-Life Gait Behavior in DCA

Advances in wearable sensor technologies enable not only task-based gait assessment without dedicated motion laboratory [87] but also passively remote capturing at patients' home [181]. Quantifying ataxia-specific changes during real-life gait behaviour adds ecologically validity to biomarkers which is an important aspect for regulatory processes.

However, the transfer of spatiotemporal variability measures for quantifying ataxic gait impairments into real life is complicated by the fact that real-life gait is inherently far more variable for both healthy controls and cerebellar patients. Thus, some variability measures may lose their accuracy for characterizing ataxic gait changes in real life (Fig. 11).

In a recent study, we identified measures of ataxic gait that allowed not only to capture the gait variability inherent in ataxic gait in real life, but also demonstrate high sensitivity to small differences in disease severity [181]. In detail, the gait measures lateral step deviation and a compound measure of spatial step variability (consisting of lateral step deviation and step length variability) (i) categorized patients against controls with a discrimination accuracy of 0.86 and (ii) both were highly correlated with clinical ataxia severity (effect size 0.76). These measures allowed detecting group





**Fig. 11** Results of the analysis of tandem walking in preataxic mutations carriers of SCA 1,2,3 and 6 [86]. Shown are relationships between genetically estimated time to onset [189] and step length variability in tandem gait conditions with and without mattress for preataxic mutation carriers MC SARA<3. The black lines represent a

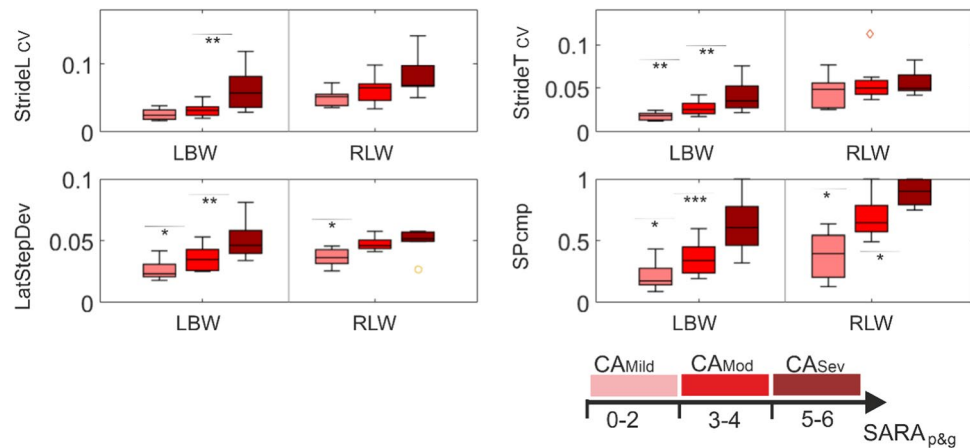
linear fit of the data; the average changes per year are indicated by the symbol ( $\Delta$ ). P-values indicate significant correlations between durations to estimated disease onset and movement parameters. Adopted from Ilg et al. [86] with permission

differences even for patients who differed only 1 point in the SARA posture & gait subscore (Fig. 12).

In conclusion, Objective biomarkers of cerebellar-induced gait changes gain increasing interest for upcoming therapeutical trails in inherited forms of DCAs. Measures quantifying cerebellar-induced gait variability suggest a high potential as treatment response marker in upcoming trials as they have shown (i) to be sensitive to disease severity in manifest as well as in preataxic stages of disease and (ii) to capture treatment-induced improvements in

neurorehabilitation studies. In addition, they allow (iii) to quantify real-life ataxic gait, thus yielding promising ecologically valid outcome measure.

Despite the high potential of the described gait measures, some limitations still exist, which should be addressed by future studies: Most results are based on mono-centre cross-sectional studies (with exception of longitudinal studies by [190, 191] and [147], whose findings should be confirmed by larger multi-centre longitudinal studies with ideally homogeneous patient populations.



**Fig. 12** Results of spatial variability measures in laboratory-based walking assessment (LBW) and real life walking behaviour (RLW) for different measures quantifying spatio-temporal variability [181]: Stride length variability (StrideL CV), Stride time variability (StrideT CV), Lateral step deviation (LatStepDev) and a compound measure of spatial variability (SPcmp), combining Stride length variability and Lateral step deviation. Shown are differences between subgroups of cerebellar patients stratified according to gait and posture

ataxia severity as determined by the SARAp&g subscore. While all variability measures differentiate between subgroups in the lab-based condition LBW, only the compound measure SPcmp differentiate between subgroups in the real-life condition RLW. Subgroups: CAMild: SARAg&p [0:2], CAMod: SARAg&p= [3-4], CASev: SARAg&p [5 - 6]. CV: Coefficient of variation. Adopted from [181] with permission

Further important aspects of future studies include:

- (i) The analysis of test–retest reliability,
- (ii) The development of multi-variate measures combining different gait features (and possibly different gait tasks)
- (iii) A more complete analysis of patients' real-life behaviour including complex movements like turning or stand-up to walk transitions, which might be in particular promising for the quantification of preataxic changes.

## Ataxic Gait and Essential Tremor

Essential tremor (ET) is one of the most prevalent movement disorders, affecting an estimated 7 million people in the USA [192]. In addition to its hallmark feature, kinetic tremor, patients may experience a range of other motor and non-motor features, many of which are linked to cerebellar dysfunction and, ultimately, underlying cerebellar degeneration [193]. One of these features is ataxic gait [194, 195].

### What Features of Gait Ataxia Are Seen in ET?

Gait impairments in cerebellar ataxia have been well characterized, and include reductions in speed, cadence, step length, and stride length as well as increases in step width, double limb support duration, step time, gait variability and trunk instability [5]. Increases in gait variability and dynamic imbalance may be due to cerebellar damage, whereas increased step width and reduced step length may represent compensations for trunk instability and imbalance [5].

The presentation of gait ataxia in ET is similar to that discussed above. Commonly reported impairments are reduced speed and cadence, impaired dynamic balance (i.e., increased double limb support duration), and asymmetry in temporal measures of gait [195, 196], 2019). While ET patients demonstrate impairments in gait speed and dynamic balance, timing control of gait does not seem to be impaired. This was demonstrated in a study in which ET patients and controls were able to match their step frequency with that of a metronome [197]. Similar results have been reported in other patients with cerebellar ataxia—timing control impairments were not seen during continuous movements [88]. These results are in agreement with the hypothesis that the cerebellum may be involved in timing control of discrete movements rather than continuous and rhythmic movements [196].

### Severity of Gait Ataxia in ET

Gait ataxia in ET can manifest with varying severity. While in many cases mild, we presented exemplar cases with

moderate gait and balance impairments, indicating that the range is considerable [198]. Examination of tandem gait impairment revealed that 18% of ET patients, in a cohort of 122 with a mean age of 64.9 years, had three or more mis-steps and 29% had two or more mis-steps [199].

### Prevalence of Gait Ataxia in ET

We reviewed the prevalence of tandem gait abnormality in ET across five studies; when defined as two or more mis-steps on tandem gait, this gait abnormality was seen in 42% of ET cases and 22% of controls [88].

Data on prevalence of gait and balance impairments in patients with cerebellar ataxia are relatively sparse. In a study with 58 patients with sporadic and hereditary forms of cerebellar ataxia, more than 50% reported fall-related injuries in the last six months [200]. In a study of 317 spinocerebellar ataxia patients, over 80% presented with a walking problem as their initial symptom [171]. Thus it appears that gait ataxia is both more prevalent and more marked in these disorders than in ET.

### Gait Ataxia in ET May Result in Functional Limitations and Is Not Simply a Sub-clinical Feature

ET patients perform worse than controls on functional tasks requiring balance such as getting up from a chair, picking up objects from the floor, and reaching for objects beyond their margin of stability [201, 202]. In addition, ET patients demonstrate lower balance confidence and report a greater number of near falls than controls [201, 202] a feature that is more marked in ET patients with head and upper limb tremor [201]. Reduced balance confidence is of further clinical and functional relevance, as it has been shown in ET to correlate with a reduction in self-reported physical activity [203]. Balance impairment (greater number of tandem mis-steps), lower balance confidence and greater number of reported falls are each significant predictors of mortality in ET, which further underscores their clinical significance [204].

### Cerebellar Dysfunction and Physiology in ET

A large and growing literature links ET to the cerebellum [193, 205]. Indeed, there is abundant evidence derived from clinical, neuroimaging and postmortem studies, linking ET to cerebellar dysfunction and postmortem studies that demonstrate a range of degenerative changes in the ET cerebellum [193, 205]. Thus, it is entirely conceivable that patients with ET might evidence some degree of ataxia on neurological examination. Future work needs to further clarify the relationship between structural changes in the cerebellum and these impairments.

In summary, ET may be viewed as common form of cerebellar degeneration. A gait ataxia is seen in many patients with ET and can present with varied severity, although it is less marked than seen in the spinocerebellar ataxias as a group. Nonetheless, in ET, it is associated with worse performance on functional tasks requiring balance, reduced balance confidence, a greater number of reported falls and a reduction in self-reported physical activity. It is also a significant predictor of mortality in ET, further underscoring its clinical significance.

## Gait Ataxia and Multiple Sclerosis

Multiple sclerosis (MS) is the commonest non-traumatic cause of neurological disability in young adults in Western Europe and North America, despite having a wide incidence variability across countries.

Patients with MS (PwMS) present a variety of physical, cognitive and psychological disabilities that, resulting in functional limitations, significantly affect their daily life activities. According to population-based studies, nearly 50% of PwMS experiences mobility impairments within the first month of diagnosis, and more than 90% within the next 10 years [206].

Gait abnormalities observed in MS reflect the presence of disseminated damage of the Central Nervous System due to demyelination and neurodegeneration, and result from impaired motor control and altered proprioception. Specifically, sensory gait ataxia is clinically defined by postural instability and heel strikes, with a higher walking cadence (number of steps per minute), while cerebellar ataxia is characterized by incoordination, poor postural control, increased variability in stride length, as well as wide base of support and bent trunk position. The latter is associated with dysmetria and dysdiadochokinesia. Beyond this semiotic characterization, in real-life these features frequently overlap, as pyramidal, cerebellar and sensory impairments are seen respectively in 85.1%, 50.9% and 51.9% of patients, and most PwMS present deficit in 2 or 3 functional systems simultaneously [207]. In clinical practice, the assessment during upright stance, with the patients' eyes opened and after eyes closed, is commonly used to distinguish ataxia due to cerebellar damage from a proprioceptive deficit in the lower limbs (Romberg's test). The cerebellar and sensory systems are among the functional systems evaluated when assessing disability in MS, with increasing levels of ataxia or proprioceptive impairment contributing to the overall Expanded Disability Status Scale (EDSS) score [208]. Recently, the International Cooperative Ataxia Rating Scale (ICARS) and the Scale for the Assessment and Rating of Ataxia (SARA), which are consistently used in cerebellar neurodegenerative diseases, have been applied to PwMS with ataxia, showing good reliability and correlations with EDSS and functional system scores [209].

Balance and postural control are strictly linked to ambulation from both a pathological background and functional performance. Imbalance and lack of coordination are among the most common symptoms affecting mobility of PwMS (67%), together with weakness (81%) and fatigue (73%) [206] and their presence has been documented even in the early stage of the disease [210]. Measures of gait and balance in PwMS include clinically based tests (i.e., the 2-min walk test, the Timed Up and Go test, the Timed 25-Foot Walk test) and laboratory-based tests (static or dynamic posturography) which provide a parameter known as center of pressure (COP) movement. Prosperini et al. showed that increased trajectories of COP during standing were associated with risk of falls, atrophy of the spinal cord, supratentorial associative white matter bundles damage and atrophy of the cerebellum in PwMS [27]. Interestingly, the variability of the COP during gait, especially in the anterior–posterior direction, has been associated with the level of cerebellar impairment in PwMS and could explain 18.1% of the variance related to ataxia [207].

Furthermore, in PwMS impaired ambulation due to cerebellar involvement is associated with the presence of focal lesions and altered diffusivity indexes within cerebellar peduncles, whose damage seems to be strongly and specifically associated with cerebellar gait abnormalities [211]. Recently, a parameter of walking coordination known as “walk-ratio”, defined as step length divided by step rate, has been directly linked with hemispheric cerebellar volume [212]. Additionally, a combined magnetic resonance imaging and posturography study showed marked volume reduction of the sensorimotor cerebellum (anterior cerebellum and lobule VIIIb) in association with physical deficits in terms of both gait and balance features in PwMS [213]. If this is true for the relapsing–remitting phase of the disease, the relationship between gait impairment and anterior cerebellar damage seems less relevant in patients with a progressive disease course [214], where, possibly, damage of other districts, such as spinal cord [215] and deep grey matter nuclei [216], become the major contributor to disability progression in terms of walking dysfunction.

Treatments for MS is based on the use of immunomodulatory therapies, which aim to reduce the overall burden of disease mainly acting on the inflammatory component of the demyelinating disorder. However, as there is no effective pharmacological treatment to manage ataxic gait in MS, neuromuscular rehabilitation [217] remains the only strategy to limit the impact of this dysfunction on patients' quality of life. Encouraging myelination-related processes along the bilateral superior cerebellar peduncles [218, 219] and augmented connectivity of the cerebellar network [220], correlated with improved clinical measures, have been detected after balance training with active exergames. To date, rehabilitative approaches enhancing neural plasticity, i.e. the capability of the brain to structurally and functionally adapt itself in response to external stimuli,

environmental changes, or injuries, represents the most promising therapeutic approach for gait ataxia in MS.

## Orthostatic Tremor and Gait Ataxia

Orthostatic tremor (OT) is a rare movement disorder characterized by a sensation of unsteadiness and high frequency tremors (13–18 Hz) present upon standing. Both symptoms disappear or improve substantially by sitting, walking or leaning [221]. Ataxia seems to be common in Primary Orthostatic Tremor [222], and there are pathophysiological, physical examination and other associations that point to a relationship between OT and the cerebellum.

## OT Pathophysiology and the Cerebellum

Large structural cerebellar abnormalities have not been consistently reported in most patients with OT. However, the most likely location of the tremor oscillator is thought to be in the posterior fossa [223]. Moreover, cerebellar activation has been shown as altered in PET and fMRI studies at rest [29, 224], and diffusion tract imaging and voxel based morphometry revealed structural changes in cerebellar white and grey matter and in components of the fronto-thalamic cerebellar circuit ([29] Benito-Leon et al., 2019).

## Presence of Ataxia in OT

Cerebellar dysfunction has been recently described in OT in prospective studies with different methodologies studying blink reflex [225], limb ataxia, and balance and postural dysfunction [222, 226]. At least mild appendicular ataxia seems very common in patients with Primary OT [222]. In a prospective study of 34 subjects with EMG-confirmed OT who underwent multiple ataxia tests, it was shown that truncal and gait ataxia was common [222]. In the same study using multiple, detailed, standardized stance and gait examination techniques, OT patients were found to have abnormal truncal sway (28%), tandem gait (61%), wide base stance (82%), and positive pull test (70%).

Although falls are not common, balance has been consistently found to be abnormal in patients with OT. In a blinded, prospective study, Functional gait assessment (FGA) and Dynamic gait index (DGI) scores were abnormal in patients with OT versus controls [227]. In another study using validated smartphone accelerometer-based measurements, there was objective evidence of imbalance in OT while standing and walking [228].

Clinically, gait in OT resembles cerebellar gait with its wide base [229, 230]. Sensor-based gait analysis showed increased temporal stride variability, a hallmark feature observed in cerebellar ataxia. Interestingly, gait was most impaired in slow

walking and improved with increased walking speed [229] in line with another study showing habitual and fast gait speeds similar to controls [227]. This resembles a proprioceptive or vestibular deficit, which could be explained in part by OT tremor's phase-dependence, predominantly present during the stance phase of ambulation [230]. Similar to most ataxias, the gait dysfunction can slowly progress over time. Falls and the use of gait aids were the only symptoms that increased (from 33 to 67% and from 6 to 44% respectively) in a 6 year cohort study of initially 34 patients [231].

## Other Important Associations

The association of OT with many illnesses of the cerebellum and its pathways and OT is present in the literature. Among many aetiologies, secondary OT has occurred in individuals with cerebellar cortical degeneration, SCA2, and SCA3 [232, 233]. Also, OT has been associated with multiple diseases that affect the spinal cord, nerve roots and other structures that could lead to cerebellar deafferentation [223].

## Is the Gait Impairment in OT Caused by Cerebellar Dysfunction?

Although it seems clear that the cerebellum and its pathways are affected in OT, it is not clear if the entirety of the gait dysfunction can be explained by this. The gait abnormalities could be due to leg tremors, abnormal proprioceptive integration, basophobia, anxiety, cerebellar ataxia, sensory ataxia, or a combination of multiple factors.

In cerebellar ataxia, stride variability is worse in slow and in fast speed as compared to preferred walking speed [234], whereas in OT, stride time coefficient of variance was increased in slow speed and normalized in preferred and fast walking speed [229]. Also, in patients with progressive cerebellar ataxia, falls are more common and more consequential [235]. Maybe OT tremor itself alters proprioceptive signaling to the CNS and therefore produces a sensory ataxia, in line with gait deterioration without visual control [229].

OT patients could be a great model to study gait and balance for many reasons, including that they can reliably activate the abnormalities at will. However, there are several challenges. The patients are normal unless standing, which limits some of the imaging modalities. Also, ataxia and balance scales have not been validated in patients transitioning within seconds to tremor.

## Unresolved Items

What's driving the progression of OT symptoms? Is it the worsening of tremor, ataxia or fear of falling? Since falls are relatively rare in patients with primary OT, is this a disease of instability or a disease of the sensation of instability?

**Table 2** Unsolved questions

Topic	Questions
OT Pathophysiology and cerebellum	What is the role of the cerebellum in generating the OT tremor? Is the sensation of instability inducing the tremor, or the tremor inducing the sensation of instability? Or are these core symptoms both caused by an epiphenomenon linked to the cerebellar dysfunction?
OT pathophysiology and proprioceptive/sensory ataxia	Does OT alter proprioceptive signaling to the CNS and therefore produces a sensory ataxia?
Progressive gait dysfunction in OT	What is driving the progression of OT symptoms? Is it the worsening of tremor, ataxia or fear of falling?
Falls in OT	Since falls are relatively rare in patients with primary OT, is this a disease of instability or a disease of the sensation of instability? Do current scales and tools differentiate instability from fear of falling -and reliably- in OT patients?
Gait in OT and cerebellum	Is the gait impairment in OT caused entirely by cerebellar dysfunction? Is there an underlying structural cerebellar deficit? Is the cerebellar dysfunction a primary or a secondary process in OT's pathogenesis?
Basophobia and gait ataxia in OT	Fear of falling could affect performances on gait and balance testing. Clinical scales have not considered this variability An objective test that measures instability in a pure fashion, and is not affected by fear of falling, would be an important advance in the field

Fear of falling could affect performance on gait and balance testing, and clinical scales have not considered this variability. An objective test that measures instability in a pure fashion, and is not affected by fear of falling, would be an important advance in the field (Table 2).

Larger long-term prospective studies are needed to understand truncal ataxia and its relationship to OT.

## Training and Gait Ataxia

There is a general agreement that the main role of the cerebellum in locomotion is to maintain gait and balance while coordinating the body segments [236]. Cerebellar dysfunctions typically result in gait ataxia, i.e., disorders in balance and coordination [5, 73]. Ataxic gait is characterized by slower walking speed, increased step width and variability, abnormal oscillations of the trunk, uncoordinated walking pattern, irregular foot trajectories, and reduced stability [5]. People with cerebellar ataxia (PwCA) suffer both physiologically and psychologically, i.e., clumsiness of gait despite normal muscle strength and frustrating lack of motor coordination during activities of daily living [187, 237]. The impaired motor control results in a significant increase in fall risk [182].

An often debated question in cerebellar ataxia is if motor training will improve balance control during locomotion-related tasks. To address this question, several authors have investigated the effect of perturbation-based balance training using trial-and-error practice [236]. Prior studies have investigated the effects of surface translation during stance for PwCA with anterior lobe cerebral disorders [238–240]. Control of upright posture when balance is perturbed is a complex task and is a prerequisite for dynamic control of

balance during locomotion. Previous reports showed that PwCA had hypermetric postural responses, i.e., overshoot the target when attempting to counterbalance against the movements, and had prolonged muscle activity after backward and lateral surface perturbations [238–240].

Morton and Bastian explored both feedforward and feedback adaptations in PwCA while walking on a split-belt treadmill [241]. In their experiment, the subjects practiced walking first with both belts running at the same speed (baseline), then at different speeds (adaptation period), and finally at the same speed (postadaptation period). The authors concluded that cerebellar damage does not impair PwCA's ability to achieve feedback-driven adaptations (e.g., reactive adjustments of stride length, stance and swing times due to belt speed changes). However, despite the practice, PwCA did not show predictive adaptation of walking parameters.

Two recent studies from our group investigated the effects of repeated waist-pull perturbations on PwCA's gait stability and motor coordination [242, 243]. PwCA walked on a treadmill while being perturbed by a series of multidirectional waist-pull perturbations. Before and after the perturbation-based training, PwCA were asked to walk naturally on the treadmill and the whole body kinematics was assessed. The results revealed that PwCA can still rely on their learning capability to modify their gait and walk more safely, as assessed by the margin of stability. i.e., the antero-posterior distance between the velocity adjusted position of the center of mass and the base of support [242]. However, PwCA's reactive response to perturbations did not significantly improve despite the practice [242]. The second study further extended these findings and showed that PwCA can exploit the lower limb motor redundancy in accordance with the uncontrolled manifold theory to better cope with

their inherent pathology, i.e. related gait variability [243]. In addition, despite the neural disease, due to the perturbation-based training, PwCA could improve their coordinative strategy and improve foot placements across strides, minimizing the effects of impairments on their balance control during treadmill locomotion.

In a different training paradigm, PwCA performed whole body physiotherapy exercises complemented by videogames, namely exergames. These games are highly motivational, include exercises within rapidly changing environments mimicking real-world activities, and allow PwCA to train at home [244]. This training has been administered to children with progressive spinocerebellar ataxia who could still walk without the use of aids [184]. After an 8-week coordinative training, results revealed that ataxia symptoms, as assessed by the Scale for the Assessment and Rating of Ataxia, decreased while balance capabilities, as assessed by the dynamic gait index, and walking patterns, i.e. lateral sway, step length variability, goal-directed leg placement, improved significantly across children.

While these studies are limited, based on these results, we can hypothesize that:

- PwCA can properly react to unexpected external disturbances at the waist or at the feet as corrective responses are mediated by fast reflexes controlled by neural centers downstream of the cerebellum [238–240],
- PwCA still retain suitable learning capabilities to benefit from intense rehabilitation treatments [23, 244],
- PwCA can take advantage of suitable interventions aimed at both activating balance control and multi-joint coordination, while training PwCA's to rely on their visual, somatosensory, and vestibular inputs [237, 245].

In the future, novel interventions should be designed with physical interactions, such as pelvic force perturbations or surface displacements, along with virtual environments that integrate visual, somatosensory, and vestibular inputs. It is also advisable to target PwCA children at an early age and exploit their natural brain plasticity, impacting their quality of life and social participation.

## Walking Adaptation Abilities

Adapting to new changes in the environment or novel movement demands is an essential requirement governed by the nervous system for optimal locomotion [246]. Humans can adapt walking patterns through both rapid changes and slower changes to gait parameters. In the presence of new movement demands, quick adjustments are made immediately in response to a perturbation. If the new movement demand is a continuous perturbation, slower changes to

the walking pattern are also observed over time [247, 248]. Notably, adaptation is evidenced by initially observing the newly learned pattern despite removing the new demand [249]. Adaptation is a relevant component of long-term motor learning, yet it is also a critical attribute of short-term locomotor control when the flexibility of walking patterns is needed.

Various motor learning and adaptation paradigms are used to better understand locomotor control in populations with gait ataxia [250–255]. Researchers study locomotor adaptation in several ways, such as adding mass to the legs, stepping on a rotating disc, treadmill walking with perturbations, or walking while the legs move at different speeds on a split-belt treadmill. Across these different paradigms, persons with gait ataxia demonstrate various impairments in locomotor adaptation. When adding mass to the lower legs to impose gait adaptation, persons with gait ataxia adapt intralimb coordination to a lesser extent than healthy age-matched controls [253]. After some time stepping on a revolving treadmill, healthy adults stepped in a curve (rather than in a straight trajectory) when asked to step in place without visual feedback. Yet, patients with mild to moderate gait ataxia displayed reduced amplitudes of rotation, perhaps indicating alterations in the ability to adapt a novel locomotor pattern [251].

## Split-Belt Treadmill Paradigm for Studying Locomotor Adaptation

Locomotor adaptation is also studied using a split-belt treadmill paradigm (for review, please see [256]). Split-belt treadmills have two independent motors and two belts that can be operated using independent speeds. Traditionally, split-belt paradigms start with a baseline condition where the belts move at the same speed. Next, during the adaptation period on the treadmill, the user walks for an extended period with the belts at different ratios of speeds, most commonly at either a 2:1 or 3:1 ratio. Then, the belts return to the same speed used during baseline. During the initial part of adaptation, interlimb parameters such as step lengths are asymmetric such that the leg on the slow belt takes a longer step. Over time, the user adapts their steps to become more symmetric, despite the belts remaining at an asymmetric ratio. When the treadmill belts return to symmetric speeds, the user displays asymmetric step lengths again, with the leg on the fast belt taking a longer step.

## Locomotor Adaptation Performance Relates to Gait Ataxia Severity

A growing body of literature recognizes that locomotor adaptation impairments are related to the severity of gait ataxia [252, 241, 255]. A well known, early study by Morton and Bastian [241] established that persons with severe gait

ataxia and cerebellar damage are unable to adapt walking patterns on a split-belt treadmill compared to healthy controls. Interestingly, persons with severe gait ataxia could adapt parameters related to the coordination within one leg similar to the healthy control group. However, persons with severe gait ataxia did not adapt interlimb parameters (i.e. the coordination between both legs) relative to the healthy control group. Unlike Morton and Bastian [241], Hoogkamer and colleagues [252] observed that interlimb parameters were not different between persons with mild gait ataxia and the healthy control group during adaptation. The likely cause for differences between studies is explained by the severity of ataxia in the patient populations. Statton and colleagues [255] verified this expected relationship between ataxia severity and locomotor adaptation ability. Persons with severe ataxia displayed deficits in the interlimb parameter compared to healthy controls. Persons with mild and moderate ataxia were able to adapt step length similar to healthy controls. Taken together, the culmination of these findings suggests that the severity of gait ataxia is a crucial consideration for locomotor adaptation.

### Spatial and Temporal Control of Locomotor Adaptation in Populations with Gait Ataxia

During locomotor adaptation, adjustments in step lengths occur by adapting when and where the foot is placed (referred to as spatial and temporal control, respectively) [257]. While understanding locomotor adaptation abilities in individuals with gait ataxia is a growing field, publications on understanding spatial and temporal contributions to adaptation remain few [250, 254]. Evidence for alterations in underlying temporal and spatial control in populations with ataxia have been mixed. Persons with mild ataxia could adapt gait on a split-belt treadmill, and underlying temporal and spatial components of step length were not different from healthy controls [255]. In persons with moderate ataxia, only temporal components were impaired, despite displaying a typical adaptation pattern. The group with severe gait ataxia exhibited impairments in the overall adaptation pattern and spatial and temporal contributions compared to healthy controls. In addition to observations in a population with cerebellar damage, persons with Essential Tremor also display altered temporal control during split-belt walking adaptation. In persons with Essential Tremor, another population that can display ataxia, overall adaptation was preserved [254]. Yet, persons with Essential Tremor displayed reduced temporal contributions to step length adaptation. Although taken together, these studies reveal underlying impairments in the control of spatial or temporal coordination during walking adaptation, research has yet to systematically investigate how spatial and temporal control is affected in populations with gait ataxia. Further work is also needed to understand if gait ataxia severity is linked to spatial and temporal control of gait adaptation.

## Gait Ataxia and Robotic Gait Training

Locomotion is an important human ability that affects an individual's life, bringing not only physical and psychosocial implications but also heavy social-economic consequences. Thus, it is fundamental to find means to promote functional walking, especially in patients with gait ataxia.

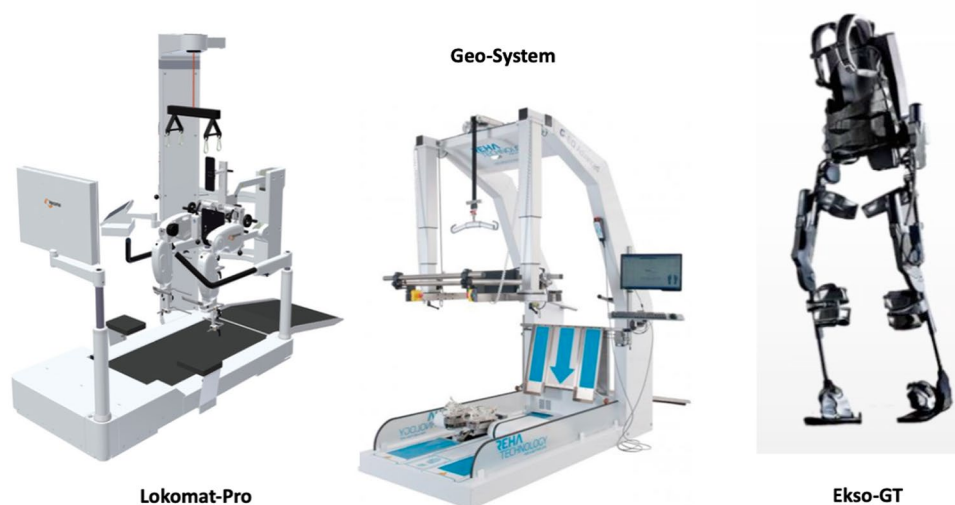
Rehabilitation interventions include conventional coordination and balance training, muscle strengthening, cycling training, exercises with technology-assisted biofeedback, compensatory orthotics and aids, respiratory muscle training and treadmill training with or without body-weight support or with perturbations [237, 242, 258].

It has been shown that neurorehabilitation may be effective to improve function, mobility and balance in genetic degenerative ataxia [258] as well as in other ataxias due to cerebellum lesions [237]. Innovation technology, applied either as assistive device or rehabilitation tool, seems promising in managing gait ataxia. Among the others, a smart walker is under evaluation to serve as a functional compensation and assist-as-needed customized rehabilitation tool. This is able to autonomously adapt the assistance to the user's need through a novel combination of real-time multimodal sensory information from advanced sensors [259].

The robotic rehabilitation systems can be classified into:

- i) Stationary systems that use fixed structures combined with a moving ground platform, and have been developed with the aim to automate the traditional therapies focusing on treadmill training. According to the types of mobile platform adopted, they can be further distinguished into treadmill gait trainers (such as the Lokomat, Fig. 13 left) and programmable foot end-effector trainers (such as the Geo-system, Fig. 13 left).
- ii) Overground walking systems (such as the Ekso-GT, Rewalk and Indego) that help the patients to practise gait, postural and balance exercises in a safe controlled manner (Fig. 13, Middle), and allow them moving under their own control rather than through predetermined movement patterns [260]. Regardless of their design, robotic rehabilitation devices are typically based on the so-called phenomenon of motor learning resulting from intensive, repetitive, and task-oriented motor activities that require patient's effort and attention [261]. In this way, the patient can practise all walking movements in a physically correct manner and this induces improvements of motor and premotor cortex representations (neuroplasticity), recovers and strengthens the capabilities of the muscle groups and improves coordination. This is why robotic-assisted gait training (RAGT) could be particularly useful in ataxia.

**Fig. 13** This figure shows the most commonly used robotic systems (ie the stationary exoskeleton Lokomat, the end-effector Geo-system and the overground exoskeleton Ekso-Gt) to treat gait disorders in neurological patients



Although RAGT showed that patients affected by stroke (especially those more severely affected and within the first 3 months of the stroke onset) had statistically significant improvement in walking speed, functional abilities, and motor functions after the treatment [262], no consensus still exists for its use in clinical practice [263].

Kim et al. in their randomized cross-over clinical trial demonstrated the effect of RAGT on balance and lower extremity function among patients with ataxia due to infratentorial stroke [264]. They found that RAGT in addition to conventional training resulted in significantly greater improvements in standing and balance function than the same amount of conventional treatments. These promising effects of RAGT can be explained by several possible mechanisms, including somatosensory facilitation, loading and latero-lateral weight shifting resulting in symmetrical gait patterns, as well as rebalance in lower limb muscle activities.

Moreover, it has been found that chronic stroke patients with ataxia had a significant improvement in balance and independence in activities of daily living after treatment with RAGT [265]. However, when the outcomes, including SARA scores, were compared between groups (i.e. RAGT and conventional treatment), there was no statistically significant difference. The authors then concluded that both trainings should be considered as options in balance rehabilitation programs for ataxic patients [265].

The use of noninvasive brain stimulation, a set of technologies and techniques to stimulate or alter brain activity from the surface of the head, could also be promising [266], especially when coupled to robotics [267]. In a recent case study, we applied a metaplasticity protocol, combining the effects of RAGT (using the Lokomat) and cerebellar tDCS to “modulate” cerebello-motor connectivity and, consequently, motor outcomes in a patient with Friedreich Ataxia. After this novel approach, the patient achieved functional improvements in gait, sitting, stance and heel-shin slide,

besides cerebellar-brain inhibition -CBI (an objective TMS measure of ataxia severity), when provided with anodal- and cathodal-tDCS plus RAGT, compared to the stand-alone RAGT [267]. Such an improvement was probably due to the restoration of functional connectivity in the cerebellum-brain networks. In fact, it could be hypothesized that tDCS over the lateral posterior cerebellar cortex may have reestablished the information flow across the deep cerebellar nuclei, the thalamus, and the sensorimotor network, probably related to LTD/LTP-like plastic changes involving Purkinje cells and postsynaptic changes of GABA receptors in the dentate nuclei and thalamus [268]. This combined approach could be used in patients with ataxia due to other neurological disorders including stroke, to restore the dysfunctional gait pathways.

In conclusion, RAGT seems effective to improve ataxia in several neurological disorders, especially when it is provided in add-on to conventional training and/or neuromodulation.

Future studies are needed to establish specific protocols (number of repetitions, time of therapy, frequency and duration of the training) in the different neurological diseases and to evaluate long-term outcomes of patients with gait ataxia.

## Dynamic Movement Orthoses

Recent advances in orthotics and fabric technology allowed to develop soft and elastic wearable devices such as knee and ankle sleeves, shorts and suits that can assist and drive human motion. These wearable devices are made of Lycra or similar elastomeric fabrics and are planned to overcome some of the limitations of the commercially available rigid orthoses (e.g. AFOs, KAFOs, hand splints), allowing to stiffen and stabilize joints, to conservatively store and return energy by means of passive spring-loaded elements and to stimulate proprioception, without restricting the joint movements.



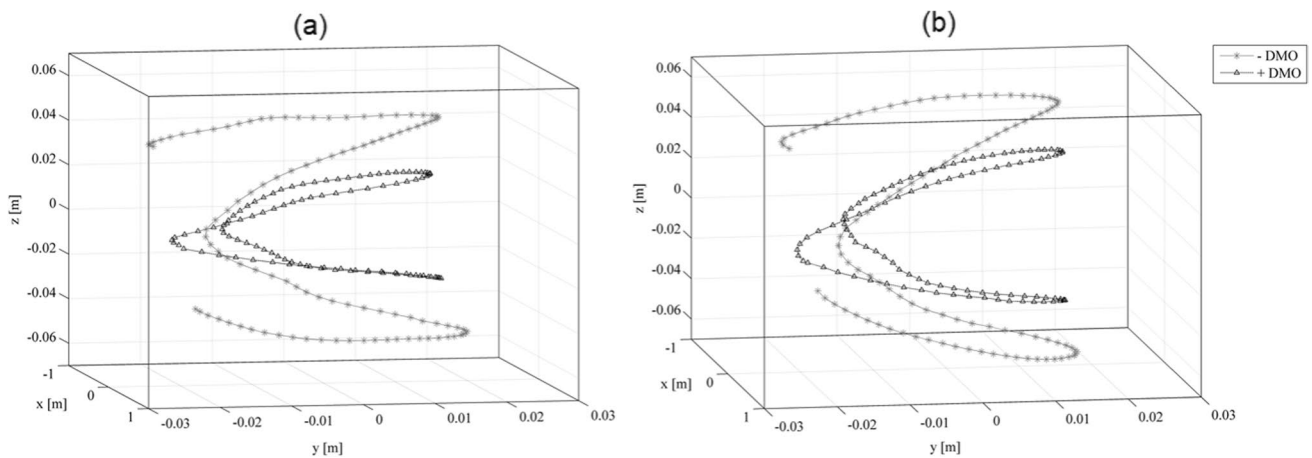
Although the scientific evidence is still limited [269], dynamic movement orthoses have been used in several neurological and orthopaedic diseases, in both children and adults, for arms [270], lower limbs [271] and for whole body [190, 272, 273]. Gait analysis studies have shown that wearable dynamic movement orthoses (DMO) can improve gait parameters [190, 271, 272], suggesting a potential role in assisting and driving gait.

Ataxic gait is known to essentially reflect poor limb coordination and impaired balance and consequent adaptive and compensatory strategies adopted by patients to maintain stability during walking [6, 175, 177, 274]. This lack of coordination reflects inability of the cerebellum to process multi-sensory features and provide an “error-correction mechanism” [80]. It leads to an abnormal intra-limb joint coupling during walking, in terms of both joint movements and interaction torques [6, 8]. In particular, increased temporal variability of intra-limb coordination has been found to be related to dynamic balance impairment and irregular foot

trajectories and foot placement on the ground [55, 154, 175]. Furthermore, the impaired inter-joint coordination leads to extremely irregular alternating joint behavior without evidence of the synchronous alternating proximal/distal joint pattern seen in healthy controls [177]. Finally, upper and lower body coordination is also affected. Patients with CA show poor intersegmental coordination, with chaotic coordinative behavior between trunk and hip compared to healthy subjects [275], leading to increased upper-body oscillations that further affect gait performance and stability [55, 152, 276]. Thus, a sort of vicious circle transforms upper body into a generator of perturbations.

Based on the above-mentioned considerations, the DMO have the potential effect to stabilize the lower limb joints and trunk without restraining their movements. Serrao et al. [190, 191] evaluated the effect of elastic orthoses designed as suits with a snug fit in a sample of 11 patients with SAOA and SCA. The suit was planned to produce resistance to the joints by the intrinsic properties of Lycra fabric (Fig. 14). Extra layers of reinforcing material and diagonal and lateral seams from the shoulder to the pelvis were added to constrain and stabilize trunk and hip joints on all spatial planes. The DMO suit was custom designed for each patient according to his/her anthropometric measurements. Gait analysis showed that, when patients wore the DMO suit, after 1 month of training, they showed a decrease in body sway, trunk oscillations (Fig. 15) and pelvis range of motions as well a reduction of double support phase and swing variability and an increase in swing phase and knee range of motion. These findings suggested that stabilizing trunk, pelvis and limb joints movements allowed patients to reduce some compensatory walking strategies (i.e. double support and swing duration) and to improve the control of

**Fig. 14** Dynamic movement orthosis (DMO) designed as elastic suit made in Lycra fabric and worn by a patient with ataxia (data from Serrao et al. [190])



**Fig. 15** Three-dimensional representation of the center of pelvic (a) and trunk (b) displacements in a representative ataxic patient with (DMO+) and without (DMO-) dynamic movement orthosis (data from Serrao et al. [190]). Patient was first recorded without DMO

(DMO-) and then he was recorded again while wearing the DMO (DMO+) after one month of having used it for 2-6 hours a day and 3-5 days a week

knee flexion during the swing phase. Since most patients also subjectively rated as high their level of satisfaction in using DMO suit, these wearable elastic suits should be considered as a potential option to improve gait stability in ataxic gait. Furthermore, DMOs seem to be more easily accepted by patients in early to moderate stages of disease, because their use is less burdened by social visibility of disability as canes or wheelchairs usually are.

However, controlled and randomized trials on a larger ataxic population are needed to increase the level of evidence on the efficacy of the DMOs in ataxic gait. The continuous advancement of wearable fabric technology should further encourage researchers and clinicians to create DMO for assisting and improving gait in patients with ataxia.

## Conclusions and Perspectives

Since Luigi Rolando and Marie-Jean-Pierre Flourens, the understanding of ataxic gait has markedly increased. The panel of experts agree that cerebellum plays a major role in human gait and balance. Cerebellar vermis, the anterior lobe in conjunction with premotor structures and lobules 6 and 7, especially crus I-II, are critical for gait and postural control. Several encephalic centers, including the cerebellar circuitry, contribute to locomotor planning, initiation and adaptation based on proprioceptive, exteroceptive, visual and vestibular feedback, while interconnected spinal cord modules regulate rhythms and patterns of flexor/extensor activities. Compelling evidence also suggests a shared circuitry between cognitive and balance systems. The cerebellum ensures the mapping of sensory information into temporally relevant motor commands, contributing to a cross-modality contextualization of sensory events. Muscular activities in cerebellar patients show impaired timing of discharges, affecting the patterning of the synergies subserving locomotion. Finally, compelling evidence suggests a shared circuitry between cognitive and balance systems, opening the field of balance training in cognitive rehabilitation.

Ataxic gait is amongst the first cerebellar deficits in cerebellar disorders such as degenerative ataxias and its evaluation may be added as a marker for the response to therapies in future trials. Features of ataxic gait are not restricted to inherited ataxias and are also observed in various neurological diseases including essential tremor, multiple sclerosis due to cerebellar and spinal cord involvement, and orthostatic tremor due to the participation of the cerebellum in the tremor network.

While clinical features of ataxic gait are well-known, the assessment of gait remains a matter of research. Early stages of cerebellar disorders can be assessed by tandem gait, a sensitive and easy to perform clinical test. The task necessitates motor predictions, coordinative timing and synergy

functions. Impaired inter-joint coordination and enhanced variability of gait temporal and kinetic parameters can be grasped by wearable devices such as accelerometers. Kinect is a promising low-cost technology to obtain reliable measurements and offers the possibility of « at-home » assessments of gait. Deep learning methods, a technology widely spread nowadays in daily life, are being developed for gait features.

Ataxic gait is one of the most disabling conditions affecting cerebellar patient. Rehabilitation interventions remain the classical therapy to compensate for ataxic gait. Static and movable robotic training are a promising approach to complement conventional rehabilitation especially when added on to conventional training and/or neuromodulation of the cerebellum. Wearable dynamic orthoses represent a potential aid to assist gait, reducing body sway, stabilizing the trunk and lower limbs without restraining the movement.

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## Declarations

**Ethics Approval** Not applicable.

**Consent for Publication** All co-authors provided consent to publication of the findings in medical journal.

**Conflicts of interest** M. Strupp is Joint Chief Editor of the Journal of Neurology, Editor in Chief of Frontiers of Neuro-otology and Section Editor of F1000. He has received speaker's honoraria from Abbott, Auris Medical, Biogen, Eisai, Grünenthal, GSK, Henning Pharma, Interacoustics, J&J, MSD, Otometrics, Pierre-Fabre, TEVA, UCB, and Viatrix. He is a share holder and investor of IntraBio. He distributes "M-glasses" and "Positional vertigo App". He acts as a consultant for Abbott, AurisMedical, Heel, IntraBio and Sensorion. The other authors declare no conflict of interest.

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