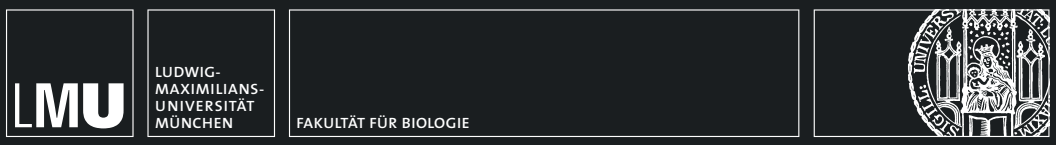

SENSORIMOTOR POSTURAL CONTROL IN HEALTHY AND PATHOLOGICAL STANCE AND GAIT

Max Wühr | Dissertation | München 2014

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DISSERTATION DER FAKULTÄT FÜR BIOLOGIE DER LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN ZUR ERLANGUNG DES GRADES EINES DOKTORS DER NATURWISSCHENSCHAFTEN | ANGEFERTIGT AM DEUTSCHEN SCHWINDEL- UND GLEICHGEWICHTSZENTRUM | VORGELEGT VON MAX WÜHR | MÜNCHEN 2014

Erstgutachter Prof. Dr. Hans Straka
Zweitgutachter Prof. Dr. Anja Horn-Bochtler
Sondervotum Prof. Dr. med. Dr. h. c. Thomas Brandt

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München, den 16. Juni 2014

Max Wühr

Contents

Abstract

Postural control during standing and walking is an inherently unstable task requiring the interaction of various biomechanical, sensory, and neurophysiological mechanisms to shape stable patterns of whole-body coordination that are able to counteract postural disequilibrium. This thesis focused on the examination of central aspects of the functional roles of these mechanisms and the modes of interaction between them. A further aim was to determine the conditions of dynamic stability for healthy standing and walking performance as well as for certain balance and gait disorders.

By studying movement fluctuations in the walking pattern it could be demonstrated that dynamic stability during walking depends on gait speed and is differentially regulated for the medio-lateral and the fore-aft walking planes. Stability control in the fore-aft walking plane exhibits attractor dynamics typical for a dynamical system. Accordingly, the most stable pattern of movement coordination in terms of minimal fluctuations in the order parameter (i.e., the relative phase between the two oscillating legs) can be observed at the attractor of self-paced walking. Critical fluctuations occur at increasingly non-preferred speeds, indicating a loss of dynamic gait stability close to the speed boundaries of the walking mode. Moreover, stability control during slow walking is critically dependent on sensory feedback control, whereas dynamic stability during fast walking relies mainly on the smooth operation of cerebellar pacemaker regions. Disturbances of sensory and cerebellar locomotor control in certain gait disorders could be further linked to a loss of dynamic gait stability, in particular an increased risk of falls.

Furthermore, this thesis examined alterations in the sensorimotor postural control scheme that may trigger the experience of subjective imbalance and vertigo in the conditions of phobic postural vertigo and visual height intolerance. Both conditions are characterized by an inadequate mode of balance regulation featuring increased levels of open-loop balance control and a precipitate integration of closed-loop sensory feedback into the postural control scheme. This inadequate balance control strategy is accompanied by a stiffening of the anti-gravity musculature and is elicited by specific influences of attention and sensory feedback control.

The findings of this thesis contribute to the understanding of central sensorimotor mechanisms involved in the control of dynamic postural stability during standing and walking. They further provide relevant information for the differential diagnosis and fall risk estimation of certain balance and gait disorders.

1 Introduction

The ability to control our body's position in space relies on the complex interaction of the musculoskeletal and neural systems, collectively referred to as the *postural control system*. Human posture is inherently unstable since two-thirds of the body mass is located two-thirds of body height above the ground. Thus, even small deviations from a perfectly upright body position cause a gravity-induced torque, which acts on the body by accelerating it further away from the upright position (Peterka, 2002, Winter, 1995a). To achieve a stable postural control, the high dimensionality of the body, i.e., the high number of muscles and joints involved in postural movements, must be reduced to a system with stable and flexible patterns of coordination that can counteract postural disequilibrium (Bernstein, 1967, Turvey, 1990). Several biomechanical, sensory, and neurophysiological mechanisms and constraints act together in shaping such patterns of whole-body coordination during the behavioral tasks of quiet standing and walking.

The following introduction reviews basic biomechanical, sensory, and neurophysiological aspects of postural control for human standing and walking behavior. Hereafter, a theoretical framework for studying postural control dynamics, i.e., the *dynamic systems theory*, is presented, which allows to investigate how stable patterns of movement emerge, how they are maintained, or how they become unstable again. An important concept in describing standing and walking behavior from a dynamic systems theory perspective is the role of variability in the control of movement. Therefore, time series approaches are introduced that allow the quantification of various features of movement variability. At the end of this introduction, the scope and the aims of this thesis are delineated.

1.1 BIOMECHANICAL ASPECTS AND MOVEMENT STRATEGIES OF POSTURAL CONTROL

Postural stability depends on the control of both gravitational forces to maintain posture and acceleration forces to maintain equilibrium (Horak et al., 1997, Massion, 1992, Nashner, 1993). Acceleration forces may be elicited from within the body as a result of voluntary movement or from outside as a consequence of unexpected external disturbance (Huxham et al., 2001). Central to postural stability is the ability to maintain the body's center of mass (CoM) within the limits of the base of support (BoS) (Nashner, 1993, Winter, 1995b, figure 1A). When this condition is satisfied, the standing person can resist destabilizing influences of gravity and actively move the CoM. Hereby, the CoM is defined as the point that is the center of the total body mass. The BoS is defined as the area within the perimeter of contact between the support surface and the two feet. Finally, the center of pressure (CoP) is the center of the distribution of the total force applied to the support surface. The CoP continuously moves around the CoM to keep the CoM within the limits of the BoS (Benda et al., 1994, Hof et al., 2005). It has been proposed that postural stability depends on the relationship between the CoM and the CoP rather than the dynamics of the CoM or CoP alone (Corriveau et al., 2001, Winter, 1995a). Accordingly, the scalar distance between the CoM and the CoP at any given point of time represents the degree of stability. This distance, which is proportional to the horizontal acceleration of the CoM, is suggested to be the error signal that drives the postural control system during balance control (Pai and Patton, 1997, Shumway-Cook and Woollacott, 2012).

Postural control, even during quiet stance, is dynamic, since standing is a quite unstable task characterized by small amounts of spontaneous postural sway and periodic corrections to overcome the destabilizing influence of gravity (Nashner, 1993, Scott and Dzendolet, 1972). Dynamic stability describes the neuromuscular system's capacity to restore or maintain a function successfully, despite naturally occurring disturbances. Because quiet stance is characterized by body sway, movement strategies are required to maintain dynamic postural stability. To examine movement strategies involved in postural control, the body has been modeled as a single-segment inverted pendulum pivoting around the ankle (Geursen et al., 1976, Winter, 1995a). In the inverted pendulum model of human balance, movement around the ankle joint mainly controls body sway. More

recently, however, it was demonstrated that the body during quiet stance behaves rather like a two-segment pendulum (legs and trunk) with both in-phase and anti-phase patterns of control (Creath et al., 2005). Correspondingly, two primary coordinative movement strategies are involved in maintaining an upright stance: (1) an *ankle strategy* for low sway frequencies (<1 Hz) in which both leg and trunk segments move in phase, and (2) a *hip strategy* for higher sway frequencies (>1 Hz) in which leg and trunk segments move out of phase (Creath et al., 2005, Horak and Nashner, 1986, Nashner, 1993). Both of these movement strategies are always present during control of upright stance, but one may predominate depending on sensory information and task condition (Horak et al., 1997).

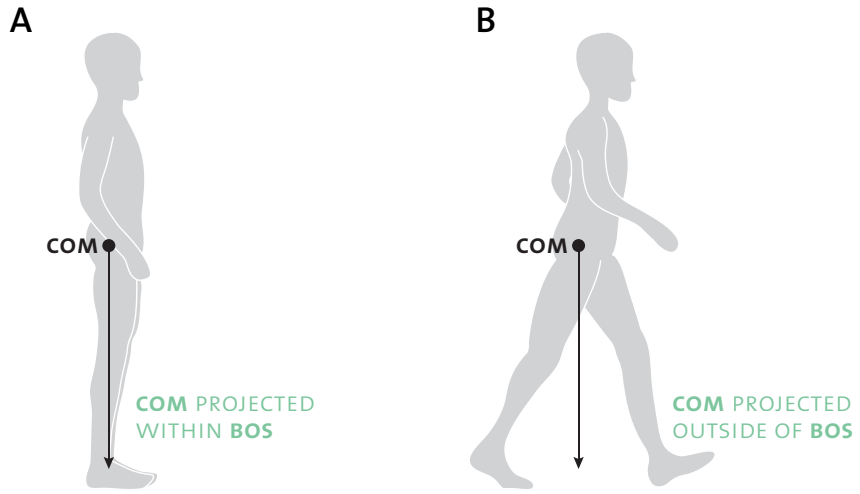

Figure 1 Stability requirements during standing and walking. (**A**) Control of postural stability while standing requires that the vertical projection of the center of mass (COM) is maintained within the base of support (BOS), defined as the area within the perimeter of contact between the support surface and the two feet. (**B**) While walking, the vertical projection of the COM falls outside the BOS most of the time and has to be recaptured by placement of the swinging limb.

Postural control, that ensures stability, is also essential for mobility tasks, such as walking. Controlling postural stability during walking is quite different and far more complex than while maintaining upright stance (Winter, 1995a). While the task during standing is to maintain the body's CoM within the BoS, the CoM during walking does not stay within the support base of the feet, and thus the body is in a continuous state of imbalance, with each step preventing a fall (figure 1B). The only stabilizing period during walking is the double-support phase, when both feet are in contact with the ground and the whole-body CoM remains within the BoS (Krebs et al., 2002, Winter, 1983).

However, for 80% of the gait cycle, postural control relies on single-support stance, during which the BoS is minimized to the width of the supporting foot and the CoM is located outside of the BoS (Winter et al., 1990, Woollacott and Tang, 1997). To prevent a fall, the swinging foot is placed ahead of the CoM as it moves forward, thereby ensuring control of the CoM relative to a moving BoS (Shumway-Cook and Woollacott, 2012). Thus, gait balance is maintained by regulating the interaction between CoM and BoS (Lugade et al., 2011). Accordingly, by modeling gait as a generalized inverted pendulum with a moveable support point, it could be demonstrated that a stable gait is achieved as a function of the CoM position and velocity at the moment of foot placement (Redfern and Schumann, 1994, Townsend, 1985). It has been proposed that as in the case of quiet standing, ankle and hip movement strategies may serve to control dynamic postural stability during the task of walking (Nashner and Forssberg, 1986, Winter, 1995a).

So far, it has been pointed out that walking and even quiet standing are dynamic processes in which the configuration of support and the relative orientation of body parts are continuously shifting due to naturally occurring disturbances and voluntary motor acts. Therefore, specific movement patterns, such as the above-mentioned ankle and hip strategies are essential to maintain dynamic equilibrium despite ongoing disturbances of postural stability. These postural movement strategies are applied in both feedforward and feedback control modes to ensure equilibrium under different circumstances (Aruin and Latash, 1995, Li and Aruin, 2007, Massion, 1992, Nashner and Forssberg, 1986, Reed-Troy and Grabiner, 2005). *Feedforward control* refers to postural adjustments that are made in anticipation of a voluntary movement (such as the voluntary displacement of the CoM during walking) that is potentially destabilizing, in order to maintain stability during the movement. In contrast, *feedback control* refers to postural responses that occur following sensory feedback (visual, vestibular, or somatosensory) from external perturbations (such as an unexpected disruption of the gait cycle due to a slip).

1.2 SENSORY SYSTEMS IN POSTURAL CONTROL

Sensory control essentially contributes to the regulation of postural stability while standing as well as walking. The effective generation and application of forces for controlling the body's position in space relies on an accurate picture of where the body is in space and whether it is stationary or in motion. Furthermore, efficient postural control requires the continuous monitoring of the reafferent sensory consequences of body movements (Paulus et al., 1984). Under normal conditions, peripheral sensory inputs from the visual, vestibular, and somatosensory systems are available to detect the body's position and movement in space with respect to gravity and the environment. Each of these sensory systems provides different information and therefore a specific frame of reference for postural control (Gurfinkel and Levick, 1991).

The visual system provides information on the position and motion of the head with respect to the surrounding environment as well as a reference for verticality (Horak and Macpherson, 1996). Movements of the body in space generate a continuously changing optic flow field on the retina, which provides information about the direction and speed in which the body is moving (Gibson, 1958, Rossignol et al., 2006). Previous research has provided several insights into the active contribution of visual feedback control on balance regulation during quiet stance. Deprivation of visual information leads to a significant increase of sway amplitude during quiet stance (Black et al., 1982, Romberg, 1853). Furthermore, stimulation with continuous or transient visual motion cues influences body sway behavior (Berthoz et al., 1979, Brandt et al., 1976, Lee and Lishman, 1975, Paulus et al., 1984). Visual information also modulates locomotion in a variety of ways and influences postural control during walking in a phase-dependent manner (Hollands and Marple-Horvat, 1996). Feedforward control by the visual system is used to regulate gait both on the local level (i.e., step-to-step basis) as well as on a global level (i.e., navigational tasks) (Patla, 1997). Visual flow cues have been shown to provide information about walking speed (Lackner and DiZio, 2000, Rossignol et al., 2006). Correspondingly, it could be demonstrated that artificially produced optic flows trigger locomotion that is perfectly adapted to the speed of the optic flow (Davis and Ayers, 1972). Besides walking speed, the absence or perturbation of visual flow information has been shown to affect numerous other aspects of the walking kinematics: head direction, cadence, stride length,

stance phase duration, swing limb trajectory, foot elevation, and upper body stability (Assaiante et al., 1989, Bauby and Kuo, 2000, Cromwell et al., 2002, Hollands and Marple-Horvat, 1996, Jahn et al., 2001, Marco et al., 2012, Patla and Goodale, 1996, Patla, 1997, Rhea and Rietdyk, 2007).

The vestibular system supplies the postural control system with information about the position and movement of the head with respect to gravity and inertial forces, thereby providing a stable gravito-inertial frame of reference for balance control (Angelaki and Cullen, 2008, Pozzo et al., 1990, Pozzo et al., 1995). By indicating the direction and velocity of sudden changes in head movement, vestibular signals are thought to trigger the onset of automatic postural responses (Horak et al., 1994b) as well as to modulate the amplitude of these responses with respect to the amplitude of the postural disturbance (Allum et al., 1993a, Horak et al., 1990, Macpherson and Inglis, 1993). The vestibular system has further been proposed to contribute to postural control via sensory reafference by determining the appropriateness and effectiveness of triggered postural responses to balance disturbances (Inglis et al., 1995). Moreover, it has been shown that the vestibular system plays an essential role in organizing the hip strategy for postural control (Allum et al., 1993b, Horak et al., 1990). During quiet stance, the absence of vestibular feedback control can be mainly compensated for by information from other sensory modalities; however a complete loss of postural equilibrium may result if visual and somatosensory sources provide inadequate orientation information (Horak et al., 1990, Nashner et al., 1982b). For navigational tasks, such as walking to a previously seen target in the dark, vestibular involvement has been demonstrated to play an essential role (Fitzpatrick et al., 1999, Jahn et al., 2000). When walking slowly, unilateral vestibular deficits result in significant deviations towards the lesioned side (Brandt et al., 1999, Brandt, 2000, Brandt et al., 2001, Jahn et al., 2000). Furthermore, there is evidence that vestibular feedback regulates the gait kinematics, in particular the timing and magnitude of foot displacement, in a phase-dependent manner (Bent et al., 2004).

The somatosensory system contributes to the postural control system by providing information about the position and motion of the body with reference to the supporting surfaces. In addition, somatosensory inputs throughout the body report information about the relationship of body

segments to one another. A loss of somatosensory input from the lower limbs is known to result in increased body sway (Diener et al., 1984, Horak et al., 1990, Magnusson et al., 1990). It could be demonstrated that two types of somatosensory information are in particular necessary to adequately signal the onset and magnitude of disturbances in postural stability and subsequently trigger adequate postural responses to restore equilibrium: (1) the muscle proprioceptors and joint afferents, which signal joint position and movement, and (2) the mechanoreceptors in the soles of the feet, which report the changing patterns of pressure and shear forces resulting from body movements (Inglis et al., 1994). Furthermore, the utilization of the ankle strategy is thought to require adequate surface somatosensory information (Gutierrez et al., 2001, Horak et al., 1990, Inglis et al., 1994). During locomotion, the somatosensory system is thought to differentially influence the walking dynamics, depending on the gait phase (Zehr and Stein, 1999). Proprioceptively mediated stretch reflexes are modulated throughout the gait cycle. At the end of the stance phase, they are facilitated in the gastrocnemius and soleus, thereby enabling compensation for ground irregularities and assisting in push-off. However, during the swing phase, they are inhibited to prevent stretch-reflex-mediated plantar-flexion during ankle dorsiflexion (Rossignol et al., 2006, Sinkjær et al., 1996). A reduction or loss of somatosensory inputs from the lower limbs results in reduced modulation of the gait dynamics, thereby affecting various aspects of the walking kinematics such as walking speed, stride time, stride length, base width, and double support duration (Allet et al., 2008, Courtemanche et al., 1996, Mueller et al., 1994)

So far, each of the sensory systems has been shown to provide important information for the regulation of balance equilibrium during quiet standing as well as walking. Maintaining postural stability essentially relies on the way in which these different sources of sensory information are processed and integrated into the postural control scheme. Previous research has suggested that sensory cues are combined in an essentially linear manner, i.e., each sensory system detects an error indicating deviation of body orientation from a reference position (Fitzpatrick et al., 1996, Johansson et al., 1988, Maki et al., 1987). More recently it could be demonstrated that sensory integration and postural regulation appear to be linear processes only for specific sensory conditions and fixed stimulus amplitudes. When stimulus conditions change, nonlinearities in these processes become

apparent (Oie et al., 2001, Peterka, 2002). Therefore, sensory contributions to postural control appear to be context-dependent (Forssberg and Nashner, 1982a, Horak and Macpherson, 1996). In line with this observation, it has been proposed that the postural control system is able to reweight sensory inputs in order to optimize balance regulation in altered sensory environments (Oie et al., 2002). Hereby, the sensory weighting implies that the gain of a sensory input will depend on its accuracy as a reference for body motion. In this view, the ability to maintain stability in a variety of environments relies on the considerable redundancy of available senses and the ability to modify the relative importance of any of these senses for postural control. Several experiments have provided evidence for the hypothesis that a sensory reweighting occurs during postural control (Brandt et al., 1998, Jeka et al., 2000, Kuo et al., 1998, Nashner, 1982a). Furthermore it was observed that in addition to external environmental factors, features of the internally driven motor program can also influence the way in which sensory information is integrated into the postural control system. Accordingly, walking speed itself affects the amount of sensory integration for locomotor control. The impact of sensory loss or perturbation decreases with increasing walking speed (Brandt et al., 1999, Brandt, 2000, Jahn et al., 2000, Jahn et al., 2001). Correspondingly, functional imaging could confirm that sensory cortex activity is decreased at faster walking speeds (Jahn et al., 2004, Jahn et al., 2008a).

1.3 NEUROPHYSIOLOGY OF POSTURAL CONTROL

Up to this point, it has been discussed how postural control during standing and walking arises from the dynamic interaction between motor strategies, which organize movements appropriate for controlling the body's position in space and sensory strategies, which process and integrate sensory information from the visual, vestibular, and somatosensory systems for adequate postural adjustments. The operation of these sensorimotor control strategies relies on the cooperative effort of many neurophysiological systems. The neural subsystems involved in postural and locomotor control are organized both hierarchically and in parallel, thereby ensuring stable system operation even if a disturbance or malfunction occurs in single subsystems (Shumway-Cook and Woollacott, 2012). Knowledge of how postural and locomotor functions are distributed within

different parts of the nervous system has been mainly derived from research on animal models of different complexity (Deliagina et al., 2006, Deliagina et al., 2007) and more recently from neuroimaging studies on human stance and gait control (Fukuyama et al., 1997, Gramann et al., 2011, Jahn et al., 2008b, Ouchi et al., 1999).

The involvement of spinal, brainstem, cerebellar, and basal ganglia circuits in mediating postural responses during standing could be demonstrated in animal models (Magnus, 1926, Sherrington, 1910) and by clinical studies in humans (Bronstein et al., 1990, Horak and Diener, 1994a, Lewko, 1996). The spinal neural circuitry by itself appears to be able to activate anti-gravity (extensor) muscles tonically for appropriate anti-gravity support (Fung and Macpherson, 1999). However, postural stability is not solely organized at the spinal level, but requires control by higher supraspinal centers like the brainstem and the cerebellum. Brainstem nuclei were shown to contribute to the regulation of anti-gravity muscle tone (Mori et al., 1989), the integration of sensory inputs for balance control (Xerri et al., 1988), the organization of anticipatory control accompanying voluntary movements (Takakusaki et al., 2004), as well as the restoration of equilibrium following disturbance of balance (Stapley and Drew, 2009). The cerebellum is an important site for the integration of sensory information into the postural control scheme (Ito, 1984). It is involved in the adaption and coordination of reactive postural adjustments based on prior practice and experience (Thach and Bastian, 2004). Furthermore, the cerebellum is thought to ensure the appropriate scaling of postural response magnitudes for anticipatory postural adjustments (Horak and Diener, 1994a, Timmann and Horak, 1997). The basal ganglia have been proposed to contribute to the ability to quickly modify muscle patterns with respect to changing task and environmental conditions. Correspondingly, it was shown that the dysfunction of basal ganglia due to Parkinson's disease results in an inability to alter the magnitude and pattern of postural responses for changes in postural demands (Beckley et al., 1993, Bloem et al., 1995, Horak et al., 2005). Therefore, it has been suggested that the basal ganglia are critical for pre-selecting a brainstem response pattern optimal for the initial conditions, with the result that an appropriate response can be rapidly triggered (Jacobs and Horak, 2007). Cortical involvement in shaping postural responses has been proposed to contribute (1) via a cerebellar-cortical loop to the adaption of postural responses based on prior experience,

and (2) via a ganglia-cortical loop to the pre-selection and optimization of postural responses based on current context (Jacobs and Horak, 2007).

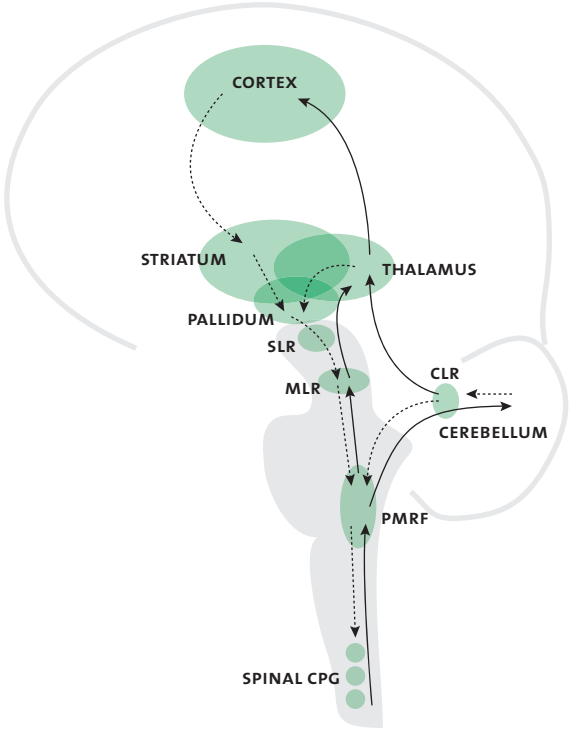

Figure 2 Diagram of the hierarchical locomotor network showing the **cortex**, the basal ganglia (**striatum**; **pallidum**), the **thalamus**, the brainstem and cerebellar locomotor regions (mesencephalic locomotor region, **MLR**; subthalamic locomotor region, **SLR**; ponto-medullary reticular formation, **PMRF**; cerebellar locomotor region, **CLR**), and spinal pattern generators (**CPG**). Descending pathways are depicted by dotted lines, ascending pathways by solid lines. Cortical signals project to the brainstem locomotor regions via the striatum and pallidum. These signals are conveyed from the pallidum via the SLR to the MLR and are further transmitted to the PMRF, where they converge with signals from the CLR. The CLR also projects signals to the MLR via the thalamus and the basal ganglia and receives input from the cerebellar cortex. The PMRF is a major site of interaction between ascending and descending pathways. Cortical signals are modulated via the basal ganglia-thalamocortical circuitry. *Adapted from Jahn et al., 2008a with reprint permission from Elsevier.*

The basic rhythmic movements of the legs and arms, which are central to locomotor pattern formation, are thought to be largely established by central pattern generators (CPG), i.e., neuronal circuits (networks of interneurons) within the spinal cord. The CPG is defined as a neural circuit that can produce self-sustained patterns of behavior, independently of sensory input (Grillner, 2003, Grillner and Wallen, 1985). Our understanding of the basic principles governing CPG function has been mainly gained from research on invertebrates, rats and cats. There is only indirect evidence for the presence of spinal CPGs in humans (Dietz, 2003). Although spinal CPGs were shown to be able to produce stereotyped locomotor patterns, descending inputs from supraspinal control

centers and sensory feedback are required for the modulation of the locomotor pattern to ensure adaptability to task and environmental conditions (Armstrong, 1988, Drew et al., 2004, Takakusaki, 2013). Animal research and neuroimaging studies of human locomotion could identify a supraspinal locomotor network that includes control centers in the brainstem, cerebellum, basal ganglia, and the frontal cortex (figure 2). Recordings from neurons in all these regions have shown the presence of rhythmical activity during locomotion. This indicates that all these sites are involved in the production of the normal walking pattern. Within this supraspinal locomotor circuitry, the initiation and termination of gait, changes in direction and velocity during walking, as well as navigational tasks are regulated (Armstrong, 1988, Jahn et al., 2008b, Shik and Orlovsky, 1976).

Brainstem locomotor centers include the mesencephalic locomotor region (MLR) and the subthalamic locomotor region (SLR). Electrical stimulation of these sites has been shown to initiate locomotion and to dictate the level of force during stepping (Drew et al., 2004). The brainstem locomotor regions receive afferent projections from the basal ganglia, the sensorimotor cortex, and the limbic system. Their descending projections reach spinal CPGs via the pontomedullary reticular formation (PMRF), the major site for interaction between descending and ascending pathways. Cerebellar locomotor regions (CLR) are thought to contribute to temporal and spatial coordination of walking movements. It has been proposed that automatic aspects of gait control are mediated via a cerebellar pacemaker region in the medial zone of the cerebellum, which receives sensory input from the somatosensory, vestibular, and visual systems and sends rhythmic outputs to the brainstem (Mori et al., 1999, Mori et al., 2001). This cerebellar pacemaker region demonstrates enhanced activity with increasing gait speed (Jahn et al., 2008a). Intermediate cerebellar zones receive afferent somatosensory input from the limbs via spinocerebellar pathways and send modulating signals to the brainstem, which are further relayed to the spinal CPGs for shaping and fine-tuning the gait pattern (Grillner and Zangger, 1979). The lateral cerebellum may play a role in adjusting gait in novel contexts and when visual guidance is disturbed (Takakusaki et al., 2008). Correspondingly, cerebellar dysfunction leads to ataxic gait, which is characterized by a highly variable and poorly accurate locomotor pattern including variable foot placements, irregular foot trajectories, and an unstable, stumbling walking path (Ilg and Timmann, 2013, Ilg et

al., 2007, Morton and Bastian, 2004). The basal ganglia have been hypothesized to be involved in the control of appropriate muscle tone, the modulation of rhythmic stepping movements, and the initiation of locomotion. Output nuclei of the basal ganglia send inhibitory projections to the MLR. Disinhibition of these projections has been shown to trigger gait initiation (Hashimoto, 2006). An increased output of the basal ganglia, as presumed to occur in Parkinson's disease (DeLong, 1990), has been shown to result in a suppression of locomotion and an increase in postural muscle tone (Takakusaki et al., 2011, Takakusaki et al., 2003). Cortical regions, including the premotor area and the supplementary motor area, are thought to contribute to cognitive aspects of locomotor control, visuomotor coordination during gait initiation, as well as obstacle avoidance tasks and anticipatory control of walking (Hanakawa et al., 1999, Takakusaki, 2013, Wiesendanger et al., 1987). Locomotor regions in the cerebral cortex send projections to the brainstem, forming the cortico-reticulo-spinal pathway for automated and voluntary control of locomotion (Mori et al., 2001). Additionally, locomotor cortex areas are connected to the cerebellum via the thalamus and pontine nuclei as well as to the basal ganglia via the basal ganglia-thalamocortical circuitry (Hashimoto, 2006).

1.4 POSTURAL CONTROL FROM THE DYNAMIC SYSTEMS THEORY PERSPECTIVE

So far, basic biomechanical, sensory and neurophysiological mechanisms and constraints have been discussed that are involved in shaping whole-body coordination for postural control tasks such as quiet standing and walking. The emergence of stable, coordinated patterns of movement that can counteract postural disequilibrium relies on the complex interaction between these mechanisms and constraints. In the following, a theoretical framework of motor control will be introduced that allows to determine and analyze the specific conditions under which stable patterns of movement will arise and to further examine how they are maintained or will become unstable again.

The human musculoskeletal apparatus is characterized by a large number of muscles and joints, all of which have to be controlled during the execution of coordinated postural movements. Accordingly, each movement involved in postural control comprises a state space of many dimensions;

the problem of coordination therefore is to reduce the high-dimensional state space into a state space of few dimensions by bringing into proper relation the multiple and different component parts of the motor apparatus (Turvey, 1990). Because each postural motor task involves a reduction of the numerous kinematic degrees of freedom present within the postural motor apparatus, there is an infinite number of appropriate movements that can equivalently solve this task. The problem of how the postural control system is capable of choosing among various equivalent movement solutions and of coordinating the many muscles and joints involved in a movement, was first addressed by the Russian physiologist Nikolai Bernstein: "it is clear that the basic difficulties for co-ordination consist precisely in the extreme abundance of degrees of freedom, with which the centre is not at first in a position to deal" (Bernstein, 1967). As a solution to the *degrees of freedom problem*, Bernstein hypothesized that there is no central control unit which individually regulates each free variable of the musculoskeletal system. Instead the control of coordinated movement would be distributed throughout many interacting subsystems working cooperatively together. By means of such cooperative interaction the postural control system should be able to group together degrees of freedom, resulting in emergent patterns of collective action that may simplify the control of the complex musculoskeletal apparatus. More specifically, Bernstein proposed the existence of a specific *muscle synergy* organization, in which groups of muscles are constrained to collectively act together as a unit (Bernstein, 1967, Ting and McKay, 2007). The combination of only a few of these muscle synergies should be able to make up the whole variety of movements required for postural control. The presumed presence of muscle synergies would thereby also solve the movement redundancy problem by providing a manageable repertoire of available motor reconfiguration patterns that may be selected on the basis of the specific movement context (Chiel et al., 2009). Later research has redefined Bernstein's initial conception of synergies, suggesting that synergies are not primarily used to eliminate redundant degrees of freedom but to ensure both stability (i.e., the ability to persist under various environmental conditions) and flexibility (i.e., the ability to adjust to changing internal or external conditions) of the movement patterns (Latash et al., 2007, Thelen et al., 1994).

Bernstein's theory of motor control entails an early account of the principle of *self-organization* that is central to a dynamic systems theory perspective, namely the hypothesis that out of the cooperative interaction between various subsystems, stable macroscopic collective patterns of organization can emerge without the need for a central control unit (Turvey, 1990). Self-organization thereby implies a significant reduction of the degrees of freedom of the system, which macroscopically manifests itself in an increase of order, i.e., pattern formation (Haken, 2012). The dynamic systems theory attempts to formulate general principles that capture the dynamics of self-organizing multi-component systems (Haken, 1977, Kelso, 1995). From the perspective of dynamic systems theory, the postural control network is considered a dynamical system, characterized by preferred modes of coordination that emerge from various interacting mechanisms and constraints (Beek et al., 1995, Collins and Stewart, 1993a, West and Scafetta, 2003). Thus, central to this kind of approach is the identification of such preferred modes that lawfully constrain the collective order and patterning of standing and walking movements (Richardson et al., 2007).

Within this theoretical framework, the studied system is subject to *control parameters,* which may be fixed from factors external to the system or generated from within the system itself. A control parameter is a variable that regulates change in the behavior of the whole system. Control parameters, if changed continuously, take a system through its repertoire of coordinated patterns. These patterns of whole-system coordination can be characterized by low-dimensional collective variables, so-called *order parameters* whose dynamics are function-dependent. The order parameter characterizes the system's behavior macroscopically and provides a measure for the organizational state of the system. On the one hand, the order parameter determines or – using the technical term of dynamic systems theory – enslaves the behavior of the individual components of the system. On the other, the individual components generate the behavior of the order parameter through their coordinated action. Thus, the coordinated interaction of the individual system components enables the emergence of an order parameter that in turn governs the behavior of the individual components. Dynamic systems theory refers to this phenomenon of bidirectional causation between different levels of a system as *circular causality*.

The dynamics of an order parameter ϕ can be explored with the help of a potential function $V(\phi)$ that describes the magnitude and the direction of the tendency of ϕ to change as a function of its own value (Beek et al., 1995, Haken et al., 1985). Accordingly, the equations of motion for order parameters are of the form:

$$\dot{\phi} = -\frac{dV(\phi)}{d\phi}.$$

When the time-derivative of the system is zero, the system is in equilibrium. If this equilibrium state is a (local) minimum of $V(\phi)$, then the system is stable; if not, the system is unstable. Stable equilibrium states of coordinated behavior are referred to as *attractor states* of the system (Strogatz, 2001). For each such attractor, its *basin of attraction* refers to the region in the phase space of the system in which all initial conditions converge to that attractor. Thus, when the system self-organizes itself under the influence of an order parameter, the system is attracted to one of the attractor states of the order parameter dynamics, i.e., it settles into a stable mode of behavior that it prefers over all possible modes. The stability of a specific attractor is relative to the depth of the (local) minimum of $V(\phi)$ and the steepness of the slope toward the minimal value, both of which depend on the value of the control parameter of the system (Haken et al., 1985). (Figure 3A)

As the control parameter is scaled up or down, the stability conditions of the system's behavior become altered. When the control parameter passes through a so-called *critical point*, a previously stable coordinated behavior of the system becomes unstable, and the system switches to a new stable pattern of coordination beyond the critical point (Smith and Thelen, 1993, Turvey, 1990; figures 3B and 3C). At such abrupt changes in the system's organization of behavior – also referred to as *non-equilibrium phase transitions* – one can observe (1) a sudden jump in the order parameter while continuous change takes place in the control parameter, reflecting the nonlinearity within the system's behavior, and (2) a qualitative change in the order parameter, reflecting a reorganization of the system's global behavior (Diedrich and Warren Jr, 1995, Haken, 1977). According to the dynamic systems theory, there are two early warning signals in the dynamics of a system approaching a critical point of phase transition: *critical slowing down* (i.e., slower recovery of the order parameter's dynamics from perturbations) as well as *critical fluctuations*, that is both

increased amplitudes of the naturally occurring fluctuations in the order parameter and increased autocorrelations within these fluctuations (Ives, 1995, Kelso et al., 1986, Scheffer et al., 2009). Thus, critical fluctuations of the order parameter are an essential characteristic of instabilities within the studied system. Their experimental detection provides evidence that observed patterns in the examined system correspond to attractor states and that the switching between states is due to loss of stability (Schöner and Kelso, 1988, Thelen et al., 1994).

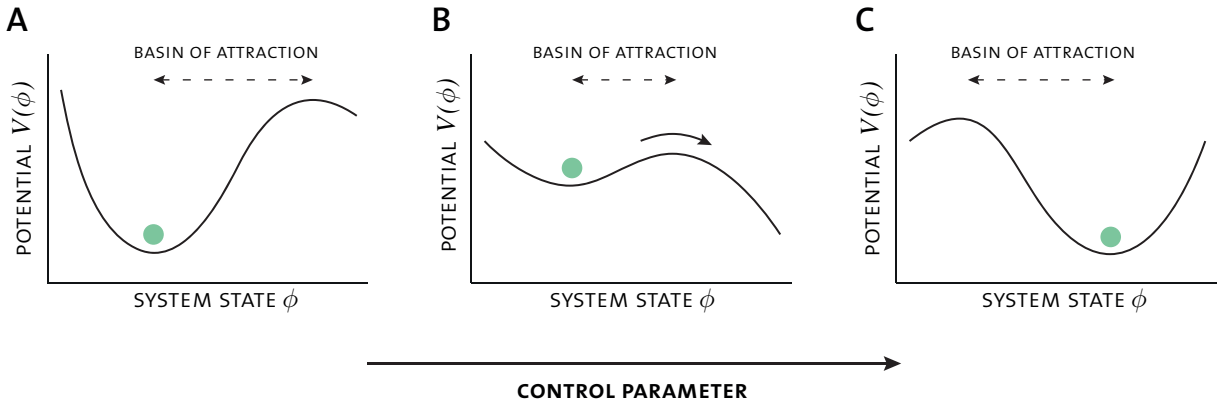

Figure 3 Concept of attractor states and non-equilibrium phase transitions. Within the framework of dynamic systems theory, the global behavior of a dynamical system is governed by a smooth potential V, that is a function of the order parameter ϕ and the control parameter. (**A**) The system is in equilibrium, when the time-derivative of the system is zero. If the equilibrium state of the system is a (local) minimum of V, then the system's global behavior is stable. Stable equilibrium states are referred to as attractor states of the system. The basin of attraction of an attractor state refers to the region in the system's phase state in which all initial conditions converge to the attractor. (**B**) If the control parameter is scaled up, the stability conditions of the system become altered, i.e., the attractor respectively the (local) minimum of V flattens and the basin of attraction shrinks. (**C**) In a non-equilibrium phase transition, as the control parameter passes through a critical point, the previously stable organization of the system's behavior becomes unstable, and the system switches to a new stable attractor state beyond the critical point. A non-equilibrium phase transition is characterized by a sudden jump of the order parameter ϕ while there is continuous change in the control parameter, and a qualitative change in ϕ reflecting the global reorganization of the system's behavior.

The above-introduced concepts from dynamic systems theory were applied in previous studies on standing and walking behavior. In the case of walking, gait velocity was identified to be a relevant control parameter of the locomotor system (Kugler and Turvey, 1987, Wagenaar and van Emmerik, 1994), because transitions between distinct gait patterns occur when the walking individual is forced to locomote faster or when electrical stimulation to certain midbrain areas is increased (Hoyt and Taylor, 1981, Shik et al., 1965). Correspondingly, the relative phase ϕ_{rel} between the oscillating legs has been suggested to be an order parameter of the locomotor system (Schöner et al., 1990). Individually preferred walking velocity was thus considered to be the attractor state of

walking behavior with respect to the dynamics of the order parameter ϕ_{rel} (Diedrich and Warren Jr, 1995). Bardy and colleagues have studied postural control dynamics during standing within the dynamic systems theory (Bardy et al., 2002, Bardy et al., 1999). They considered the relative phase ϕ_{rel} between angular movements of the hips and of the ankles as an order parameter of quiet stance behavior. This order parameter was shown to exhibit the attractor states of in-phase ($\phi_{rel} \approx 0°$) and anti-phase ($\phi_{rel} \approx 180°$) coordination. Furthermore, it could be demonstrated that changes between these stable modes of behavior feature the characteristics of non-equilibrium phase transitions, including critical slowing down and critical fluctuations (Bardy et al., 2002, James, 2014).

1.5 TIME SERIES APPROACHES FOR THE ANALYSIS OF MOVEMENT VARIABILITY

For a long time, movement variability was considered to be simply the consequence of errors in motor performance or assigned to random neural noise (Faisal et al., 2008, Hausdorff, 2005). However, by considering postural control from the dynamic systems theory perspective it has become apparent that fluctuations within a certain pattern of coordinated movement are a meaningful inherent characteristic of the motor behavior and are closely linked to the stability of the movement pattern. Furthermore, previous studies provided evidence that quantitative approaches to postural control behavior that are based on averaging movement performance over time, could conceal the control principles that underlie the observed postural dynamics and emphasized the value of movement fluctuation analysis for disclosing such principles (Hausdorff, 2005, Newell et al., 1993). Studying movement fluctuations in postural control behavior is therefore essential in order to determine both the stable attractor states and the conditions for instability in standing and walking behavior as well as the underlying sensorimotor control principles of these behavioral tasks. The following paragraphs will introduce central time series approaches used in the studies of this thesis that allow to analyze distinct complementary features of movement fluctuations in standing and walking behavior.

1.5.1 *Coefficient of variation*

The above discussion of non-equilibrium phase transitions has shown that the amplitude of fluctuations in the order parameter is an important parameter for determining the system's stability. The fluctuation amplitude can be quantified by the *coefficient of variation* (CV), which is a normalized measure of the statistical dispersion of a time series. The CV is defined as the ratio of the standard deviation σ to the mean μ:

$$CV = \frac{\sigma}{\mu},$$

and represents the extent of variability in relation to the mean of a time series.

1.5.2 *Detrended fluctuation analysis*

Besides the amplitude of order parameter fluctuations, the strength of autocorrelations within these fluctuations (i.e., the memory properties of the time series) is another central parameter for assessing the stability of the studied system. When considering autocorrelations within a time series x_k, the correlation of the values x_k and x_{k+t} for different time lags t is of interest. To get rid of a constant offset in the data, the mean is subtracted from the time series $\overline{x}_k \equiv x_k - \langle x \rangle$. The correlations between x-values separated by t steps are then quantitatively defined by the autocorrelation function (Kantelhardt et al., 2001):

$$C(t) = \langle \overline{x}_k \overline{x}_{k+t} \rangle = \frac{1}{N-t} \sum_{k=1}^{N-t} \overline{x}_k \overline{x}_{k+t} \, .$$

If the time series x_k is uncorrelated, $C(t) = 0$ for $t > 0$. The presence of short-range correlations in x_k is indicated by an exponentially declining $C(t)$, $C(t) \sim e^{\left(-\frac{t}{\tau}\right)}$ with a decay time τ. For the case of long-range correlations in x_k, $C(t)$ declines as a power-law, $C(t) \sim t^{-\gamma}$ with an exponent $0 < \gamma < 1$. However, the direct calculation of $C(t)$ is usually not reliable due to noise superimposed on the recorded time series x_k or unknown underlying trends, i.e., non-stationarities within the time series.

To evaluate the correlation characteristics within noisy non-stationary time series, a type of root mean square analysis called *detrended fluctuation analysis* (DFA) was developed by Peng and colleagues (Peng et al., 1995). The DFA method first forms an accumulated sum $Y(i) = \sum_{k=1}^{i} x_k - \langle x \rangle$ of the time series x_k of length N. This integration step has been suggested to avoid shortcomings of earlier methods (Delignieres et al., 2005). Thereafter, $Y(i)$ is divided into non-overlapping segments $N_s \equiv \left[\frac{N}{s}\right]$ of equal length s, ranging from 4 to N / 4 data points. In the next step the local trend p_v for each segment v is calculated by a least squares fit to the data and subtracted from the segment yielding the detrended time series $Y_s(i) = Y(i) - p_v(i)$ for the segment duration s. After the variance $F_s^2(v) = \left\langle Y_s^2(i) \right\rangle$ of the detrended series is calculated, the DFA fluctuation function:

$$F(s) = \left[\frac{1}{N} \sum_{v=1}^{N_s} F_s^2(v) \right]^{\frac{1}{2}},$$

for the scale s is obtained, which increases with s by a power-law $F(s) \sim s^{\alpha}$ with the scaling exponent α. The scaling exponent α gives a quantitative measure for the strength of long-range correlations within the time series. A scaling exponent α = 0.5 indicates uncorrelated data (i.e., white noise); α values between 0.5 and 1.0 indicate persistent long-range power-law correlations; the closer α is to 1.0 the greater the influence of the distant past when compared with the influence of the recent past. The case of α = 1.0 corresponds to 1/f noise, where present events are approximately equally correlated with events from the recent and the very distant past. For α > 1.0 correlations exist but cease to be of a power-law form; α = 1.5 indicates brown noise, i.e., integrated white noise. Brown noise is influenced by the recent past much more strongly than by the distant past and is therefore characterized by only local correlations (Fossion et al., 2010, Keshner, 1982, Peng et al., 1995).

1.5.3 *Phase synchronization*

As mentioned above, the phase relationship between the oscillating legs during walking has been suggested to be an order parameter of the walking behavior. To examine the dynamics of this order parameter, one can study the fluctuations within the relative timing behavior of the oscillating legs by performing a type of phase synchronization analysis (Bartsch et al., 2007b, Strogatz, 2001).

For this purpose, the phase difference between the right and left leg can be determined by using the time series of heel-strike (hs) events t_k^{hs} and toe-off (to) events t_k^{to} of the left and right foot:

$$\Delta\varphi_k^m = 2\pi \frac{t_k^{m,ri} - t_k^{hs,le}}{t_{k+1}^{hs,le} - t_k^{hs,le}},$$

where $t_k^{hs,le}$ refers to the kth heel strike event of the left leg and $t_k^{m,ri}$ either to the kth heel-strike (m=hs) or toe-off (m = to) event of the right leg. This yields the time series of phase differences, $\psi = \Delta\varphi_1^{hs}, \Delta\varphi_1^{to}, ..., \Delta\varphi_k^{hs}, \Delta\varphi_k^{to}, ...$ Since a typical result is $\langle \Delta\varphi^{hs} \rangle \neq \langle \Delta\varphi^{to} \rangle$, the time series of the normalized phase differences $\tilde{\psi} = \Delta\tilde{\varphi}_1^{hs}, \Delta\tilde{\varphi}_1^{to}, ..., \Delta\tilde{\varphi}_k^{hs}, \Delta\tilde{\varphi}_k^{to}, ...$ with $\Delta\tilde{\varphi}_k^{hs} = \Delta\varphi_k^{hs} - \frac{1}{2}(\langle \Delta\varphi^{hs} \rangle - \langle \Delta\varphi^{to} \rangle)$ and $\Delta\tilde{\varphi}_k^{to} = \Delta\varphi_k^{to} + \frac{1}{2}(\langle \Delta\varphi^{hs} \rangle - \langle \Delta\varphi^{to} \rangle)$ is calculated. In order to quantify the distribution of the phase differences, the Shannon entropy $S = -\sum_{i=1}^{N} p_i \, ln(p_i)$ is calculated from the histogram of $\tilde{\psi}$. Finally, the phase synchronization index is defined by:

$$\rho = \frac{S_{max} - S}{S_{max}},$$

where $S_{max} = ln(N)$ (i.e., a uniform distribution of $\tilde{\psi}$). According to this formula, ρ = 0 indicates no synchronization, whereas ρ = 1 means a maximal synchronization.

1.5.4 *Stabilogram diffusion analysis*

To specifically assess the correlations in experimental CoP time series during quiet standing, Collins and De Luca introduced a time series approach called *stabilogram diffusion analysis* (SDA) (Collins and De Luca, 1993b, Collins and De Luca, 1994). SDA assumes that the CoP trajectory during quiet stance can be modeled as a process of coupled, correlated random walks and analyses the diffusion properties of this process. A typical SDA shows that spontaneous body sway is characterized by a two-part behavior, indicating that open-loop control governs postural behavior over short-term intervals while long-term intervals are regulated by closed-loop control (Collins et al., 1995, Collins and De Luca, 1993). An open-loop control system operates without sensory feedback and determines the steady-state activity of anti-gravity muscles (Laughton et al., 2003). Open-loop feed-forward control thus represents the motor commands that place the body in a desired

posture. In contrast, closed-loop control relies on sensory feedback from the visual, vestibular, and proprioceptive systems. Closed-loop feedback control corrects drifts away from desired posture due to the effects of gravity, stochastic variations in muscle tone, etc. Intervention of feedback control might be triggered when CoP displacement exceeds certain boundaries (Collins and De Luca, 1993b) or when CoP velocity reaches a certain threshold (Delignieres et al., 2011). The time threshold at which postural control switches from open- to closed-loop behavior is delimited by the so-called critical point.

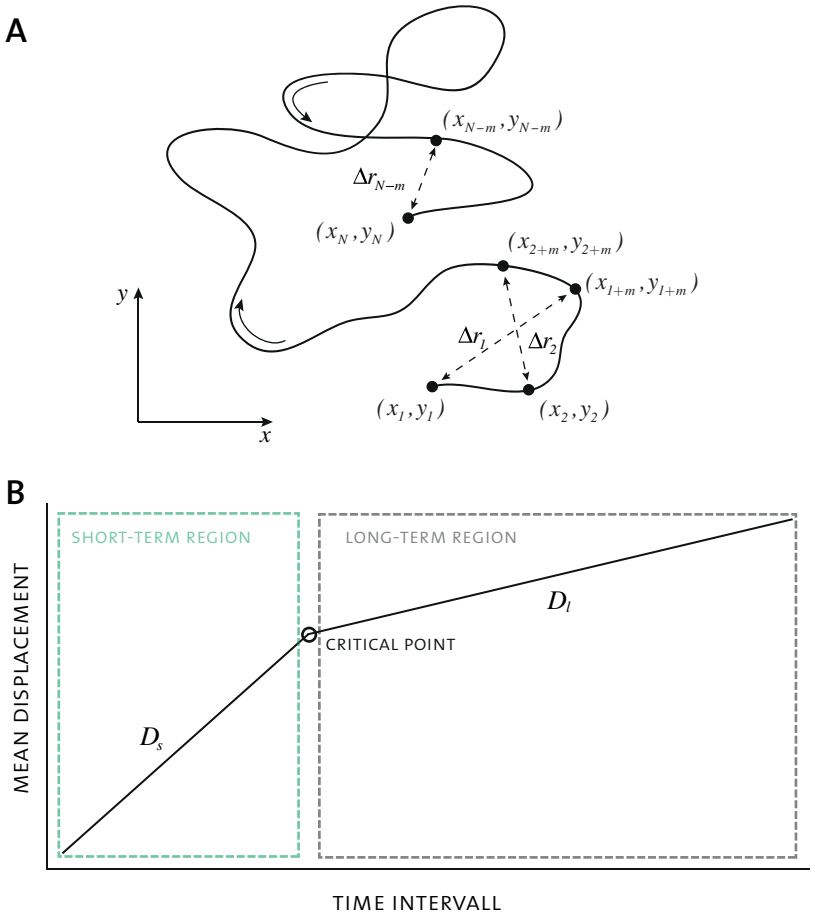

Figure 4 Stabilogram diffusion analysis: (**A**) Diagram illustrating the method for calculating the mean squared displacement $\langle \Delta r^2 \rangle$ as a function of the time interval Δt for a CoP trajectory consisting of N data points $(x_1, y_1; x_2, y_2; \ldots; x_N, y_N)$. For a given Δt (spanning m data intervals) the mean squared displacement can be calculated as follows: $\langle \Delta r^2 \rangle_{\Delta t} = \sum_{i=1}^{N-m} (\Delta r_i)^2 / (N-m)$. (**B**) Stabilogram diffusion plot ($\langle \Delta r^2 \rangle$ vs. Δt) obtained from the above-described method applied on a CoP time series. Diffusion coefficients D_s and D_l are computed from the slopes of the fitted lines to the short-term and long-term regions. The critical point is defined as the intersection of the lines fitted to the short- and long-term regions. The resulting diffusion plot reflects the two-part behavior of spontaneous body sway: over short-term intervals open-loop control governs postural behavior, while long-term intervals are regulated by closed-loop control. *Adapted from Collins and De Luca, 1993b with reprint permission from Springer Verlag.*

The CoP SDAs can be calculated with the following equation:

$$\left\langle \Delta r^2 \right\rangle = \left\langle \left[r(t+\Delta t) - r(t) \right]^2 \right\rangle,$$

where $\langle \bullet \rangle$ indicates the calculation of the mean of the time series (figure 4A). This computation is repeated for increasing values of Δt in the range of 0-10s. The resulting diffusion plot shows the mean squared displacements against the time intervals Δt. The short- and long-term diffusion coefficients $D_s(mm^2 s^{-1})$ and $D_l(mm^2 s^{-1})$ are determined by linear fits to the diffusion plot. The critical point coordinates $\Delta t_c(s)$ (critical time) and $\left\langle \Delta r^2 \right\rangle_c (mm^2)$ (critical displacement) are obtained from the intersection point of the linear fits to the short- and long-term regions (figure 4B). The scaling exponents for the short- and long-term region H_s and H_l can be determined by linear fits to the log-log plot of the SDA. These exponents, which lie in the range $0 < H < 1$, quantify the correlation between the step increments, which make up the stabilogram time series. For $H > 0.5$ past and future increments are positively correlated. For $H < 0.5$, past and future increments are negatively correlated.

1.6 AIMS OF THE THESIS

The preceding sections of the introduction highlighted the various biomechanical, sensory, and neurophysiological mechanisms involved in establishing a stable postural performance during standing and walking behavior. The studies of this thesis aim to contribute to the understanding of the functional roles and the modes of interaction of these mechanisms that make up the postural control scheme in the healthy as well as in the pathologically disturbed standing and walking performance. In addition, these studies share the attempt to shed more light on the stability conditions of postural control in the healthy standing and walking behavior as well as in certain relevant gait and balance disorders. Finally, a central endeavor of the following studies was to focus on the clinical relevance of their research findings and to connect them to the clinical praxis by (1) establishing appropriate objective measures for the differential diagnosis of certain gait and balance disorders, (2) by monitoring the effects of medical treatments by means of the established measures, and (3) by promoting fall risk estimation procedures for the investigated pathological

conditions. On the basis of the dynamic systems theory perspective on postural control, the studies presented here focus on the analysis of fluctuations within the patterns of coordinated movement during standing and walking behavior to disclose the sensorimotor principles underlying the performance of these behavioral tasks and to evaluate their stability conditions in the healthy and pathologically disturbed conditions. Especially for the case of gait analysis, the whole dynamic range of walking speed (i.e., the control parameter for gait dynamics) was considered in order to examine both the stable attractor states and the conditions for instability in healthy walkers and patients with certain sensorimotor gait disorders.

The study presented in **chapter 2.1** investigated stability control and attractor dynamics of the healthy human walking behavior by examining patterns of optimization in single- and inter-leg gait dynamics. This study tried to clarify the following key questions: How do temporal fluctuation and synchronization properties of single- and inter-leg gait dynamics depend on the walking speed and do these properties exhibit a pattern of optimization in terms of stability at the attractor of the preferred walking mode? The studies presented in **chapters 2.2 – 2.4** investigated sensory feedback from the visual, proprioceptive, and vestibular systems for the control of locomotion. Sensory feedback control is thought to play an important role in adjusting stride-to-stride trajectories to maintain balance and in smoothing unintended irregularities during walking (Gandevia and Burke, 1992, Nashner, 1980). These studies addressed the following key questions: Does sensory feedback control of locomotion depend on the walking speed? What influence does sensory feedback have on stability control during walking and what kind of gait instabilities arise due to absent or pathologically disturbed sensory feedback control of locomotion? The studies presented in **chapters 2.4 – 2.8** examined the role of cerebellar locomotor control. The cerebellum is an important relay region for sensory integration into the locomotor network and provides rhythmic input for the coordination of the walking pattern (Mori et al., 1999, Mori et al., 2001). The key questions posed by these studies were: Do cerebellar locomotor functions depend on the walking speed? What specific role do cerebellar locomotor functions play in stability control during walking, and what kind of gait instabilities arise due to disturbed cerebellar locomotor control in patients with cerebellar ataxia? These studies furthermore examined the therapeutic effects of 4-Aminopyridine on the

gait disorder in cerebellar ataxia. The studies presented in **chapters 2.9 – 2.11** examined postural control in two distinct forms of subjective imbalance and vertigo, i.e., phobic postural vertigo and visual height intolerance. Individuals suffering from one of these conditions under certain circumstances experience subjective imbalance and vertigo, despite normal outcomes in clinical balance tests (Brandt, 1996, Brandt and Huppert, 2014). These studies examined the following key questions: Do individuals suffering from subjective vertigo exhibit altered strategies of postural control and patterns of anti-gravity muscle innervation? Are these alterations due to influences of sensory feedback control, attention, and/or anxiety?

The following section (**2.1 – 2.11**) presents all studies conducted within the scope of this doctoral thesis. In the subsequent section (**3.1 & 3.2**), the key findings of these studies will be comprehensively discussed.

2 Cumulative Thesis

This cumulative thesis consists of eleven published research articles. Full papers are presented in the following and the author contributorship is stated. The complete list of publications, including those which are not part of this thesis, can be found in the curriculum vitae. The research articles are presented in the following order:

- **Wuehr M**, Pradhan C, Brandt T, Jahn K, Schniepp R. Patterns of optimization in single- and inter-leg gait dynamics. *Gait Posture*. 2014;**39**(2):733-8.

  The author of this thesis designed the experiment and performed the gait carpet and treadmill recordings, analyzed the data including the programming of the data analysis procedures, and wrote the manuscript.

- **Wuehr M**, Schniepp R, Pradhan C, Ilmberger J, Strupp M, Brandt T, Jahn K. Differential effects of absent visual feedback control on gait variability during different locomotion speeds. *Exp Brain Res*. 2013;**224**(2):287-94.

  The author of this thesis designed the experiment and performed the gait carpet and treadmill recordings, analyzed the data including the programming of the data analysis procedures, and wrote the manuscript.

- **Wuehr M**, Schniepp R, Schlick C, Huth S, Pradhan C, Dieterich M, Brandt T, Jahn K. Sensory loss and walking speed related factors for gait alterations in patients with peripheral neuropathy. *Gait Posture*. 2014;**39**(3):852-58.

  The author of this thesis designed the experiment, assisted in performing the gait carpet recordings and the fall risk assessment, analyzed the data including the programming of the data analysis procedures, and wrote the manuscript.

- Schniepp R, **Wuehr M**, Neuhaeusser M, Kamenova M, Dimitriadis K, Klopstock T, Strupp M, Brandt T, Jahn K. Locomotion speed determines gait variability in cerebellar ataxia and vestibular failure. *Mov Disord*. 2012;**27**(1):125-31.

  The author of this thesis participated in designing the experiment, assisted in performing the gait carpet recordings and in analyzing the data including the programming of the data analysis procedures, and wrote parts of the methods and discussion section of the manuscript.

- **Wuehr M**, Schniepp R, Ilmberger J, Brandt T, Jahn K. Speed-dependent temporospatial gait variability and long-range correlations in cerebellar ataxia. *Gait Posture*. 2013;**37**(2):214-8.

  The author of this thesis designed the experiment and performed the gait carpet and treadmill recordings, analyzed the data including the programming of the data analysis procedures, and wrote the manuscript.

- Schniepp R, **Wuehr M**, Ackl N, Danek A, Brandt T, Strupp M, Jahn K. 4-Aminopyridine improves gait variability in cerebellar ataxia due to CACNA 1A mutation. *J Neurol*. 2011;**258**(9):1708-11

  The author of this thesis participated in designing the experiment, assisted in performing the gait carpet recordings and in analyzing the data including the programming of the data analysis procedures, and wrote the methodological part of the manuscript.

- Schniepp R, **Wuehr M**, Neuhaeusser M, Benecke AK, Adrion C, Brandt T, Jahn K. 4-Aminopyridine and cerebellar gait: a retrospective case series. *J Neurol*. 2012;**259**(11):2491-3.

  The author of this thesis participated in designing the experiment and assisted in analyzing the data including the programming of the data analysis procedures.

- Schniepp R, **Wuehr M**, Schlick C, Huth S, Pradhan C, Dieterich M, Brandt T, Jahn K. Increased gait variability is associated with the history of falls in patients with cerebellar ataxia. *J Neurol*. 2014;**261**(1):213-23.

  The author of this thesis participated in designing the experiment, assisted in performing the fall risk assessment and in analyzing the data including the programming of the data analysis procedures, and wrote parts of the methods section of the manuscript.

- Schniepp R*, **Wuehr M***, Pradhan C, Novozhilov S, Krafczyk S, Brandt T, Jahn K. Nonlinear variability of body sway in patients with phobic postural vertigo. *Frontiers in neurology*. 2013;**4**:115.

  * equal contribution

  The author of this thesis designed the experiment, analyzed the posturography data including the programming of the data analysis procedures, and wrote the manuscript.

- **Wuehr M**, Pradhan C, Novozhilov S, Krafczyk S, Brandt T, Jahn K, Schniepp R. Inadequate interaction between open- and closed-loop postural control in phobic postural vertigo. *J Neurol*. 2013;**260**(5):1314-23.

  The author of this thesis designed the experiment, analyzed the posturography data including the programming of the data analysis procedures, and wrote the manuscript.

- **Wuehr M**, Kugler G, Schniepp R, Eckl M, Pradhan C, Jahn K, Huppert D, Brandt T. Balance control and anti gravity muscle activity during the experience of fear at heights. *Physiological Reports*. 2014;**2**(2).

  The author of this thesis participated in designing the experiment and performed the posturographic and electromyographic recordings, analyzed the data including the programming of the data analysis procedures, and wrote the manuscript.

2.1 PATTERNS OF OPTIMIZATION IN SINGLE- AND INTER-LEG GAIT DYNAMICS

WUEHR M, PRADHAN C, BRANDT T, JAHN K, SCHNIEPP R

CONTRIBUTORSHIP

WUEHR M.	**1ABCDEF	2A**
PRADHAN C.	**1A	2B**
BRANDT T.	**1ABF	2B**
JAHN K.	**1ABF	2B**
SCHNIEPP R.	**1ABCF	2B**

1 RESEARCH PROJECT: **A** CONCEPTION | **B** ORGANIZATION | **C** EXECUTION | **D** PROGRAMMING OF DATA ANALYSIS PROCEDURES | **E** DATA ANALYSIS | **F** DATA INTERPRETATION

2 MANUSCRIPT: **A** WRITING THE FIRST DRAFT | **B** REVIEW AND CRITIQUE

LINK

http://dx.doi.org/10.1016/j.gaitpost.2013.10.013

2.2 DIFFERENTIAL EFFECTS OF ABSENT VISUAL FEEDBACK CONTROL ON GAIT VARIABILITY DURING DIFFERENT LOCOMOTION SPEEDS

WUEHR M, SCHNIEPP R, PRADHAN C, ILMBERGER J, STRUPP M, BRANDT T, JAHN K

CONTRIBUTORSHIP

WUEHR M.	**1ABCDEF	2A**
SCHNIEPP R.	**1ABCF	2B**
PRADHAN C.	**2B**
ILMBERGER J.	**1B	2B**
STRUPP M.	**1A	2B**
BRANDT T.	**1ABF	2B**
JAHN K.	**1ABF	2B**

1 RESEARCH PROJECT: **A** CONCEPTION | **B** ORGANIZATION | **C** EXECUTION | **D** PROGRAMMING OF DATA ANALYSIS PROCEDURES | **E** DATA ANALYSIS | **F** DATA INTERPRETATION

2 MANUSCRIPT: **A** WRITING THE FIRST DRAFT | **B** REVIEW AND CRITIQUE

LINK

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2.3 SENSORY LOSS AND WALKING SPEED RELATED FACTORS FOR GAIT ALTERATIONS IN PATIENTS WITH PERIPHERAL NEUROPATHY

WUEHR M, SCHNIEPP R, SCHLICK C, HUTH S, PRADHAN C, DIETERICH M, BRANDT T, JAHN K

CONTRIBUTORSHIP

WUEHR M.	**1ABCDEF	2A**
SCHNIEPP R.	**1ABCF	2B**
SCHLICK C.	**1C	2B**
HUTH S.	**1C	2B**
PRADHAN C.	**1F	2B**
DIETERICH M.	**1B	2B**
BRANDT T.	**1ABF	2B**
JAHN K.	**1ABF	2B**

1 RESEARCH PROJECT: **A** CONCEPTION | **B** ORGANIZATION | **C** EXECUTION | **D** PROGRAMMING OF DATA ANALYSIS PROCEDURES | **E** DATA ANALYSIS | **F** DATA INTERPRETATION

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2.4 LOCOMOTION SPEED DETERMINES GAIT VARIABILITY IN CEREBELLAR ATAXIA AND VESTIBULAR FAILURE

SCHNIEPP R, WUEHR M, NEUHAEUSSER M, KAMENOVA M, DIMITRIADIS K, KLOPSTOCK T, STRUPP M, BRANDT T, JAHN K

CONTRIBUTORSHIP

SCHNIEPP R.	**1ABCEF | 2A**
WUEHR M.	**1ACDEF | 2A**
NEUHAEUSSER M.	**1ACD | 2B**
KAMENOVA M.	**1C | 2B**
DIMITRIADIS K.	**1AB | 2B**
KLOPSTOCK T.	**1AB | 2B**
STRUPP M.	**1BF | 2B**
BRANDT T.	**1ABF | 2B**
JAHN K.	**1ABF | 2B**

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2.5 SPEED-DEPENDENT TEMPOROSPATIAL GAIT VARIABILITY AND LONG-RANGE CORRELATIONS IN CEREBELLAR ATAXIA

WUEHR M, SCHNIEPP R, ILMBERGER J, BRANDT T, JAHN K

CONTRIBUTORSHIP

WUEHR M.	**1ABCDEF	2A**
SCHNIEPP R.	**1ABCF	2B**
ILMBERGER J.	**1B	2B**
BRANDT T.	**1ABF	2B**
JAHN K.	**1ABF	2B**

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2.6 4-AMINOPYRIDINE IMPROVES GAIT VARIABILITY IN CEREBELLAR ATAXIA DUE TO CACNA 1A MUTATION

SCHNIEPP R, WUEHR M, ACKL N, DANEK A, BRANDT T, STRUPP M, JAHN K

CONTRIBUTORSHIP

SCHNIEPP R.	**1ABCEF | 2A**
WUEHR M.	**1ACDEF | 2A**
ACKL N.	**1B | 2B**
DANEK A.	**1B | 2B**
BRANDT T.	**1ABF | 2B**
STRUPP M.	**1ABF | 2B**
JAHN K.	**1ABF | 2B**

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2.7 4-AMINOPYRIDINE AND CEREBELLAR GAIT: A RETROSPECTIVE CASE SERIES

SCHNIEPP R, WUEHR M, NEUHAEUSSER M, BENECKE AK, ADRION C, BRANDT T, JAHN K

CONTRIBUTORSHIP

SCHNIEPP R.	**1ABCEF	2A**
WUEHR M.	**1ADEF	2B**
NEUHAEUSSER M.	**1AD	AB**
BENECKE AK.	**1C	2B**
ADRION C.	**1E	2B**
BRANDT T.	**1ABF	2B**
JAHN K.	**1ABF	2B**

1 RESEARCH PROJECT: **A** CONCEPTION | **B** ORGANIZATION | **C** EXECUTION | **D** PROGRAMMING OF DATA ANALYSIS PROCEDURES | **E** DATA ANALYSIS | **F** DATA INTERPRETATION

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2.8 INCREASED GAIT VARIABILITY IS ASSOCIATED WITH THE HISTORY OF FALLS IN PATIENTS WITH CEREBELLAR ATAXIA

SCHNIEPP R, WUEHR M, SCHLICK C, HUTH S, PRADHAN C, DIETERICH M, BRANDT T, JAHN K

CONTRIBUTORSHIP

SCHNIEPP R.	**1ABCEF	2A**
WUEHR M.	**1ACDEF	2A**
SCHLICK C.	**1CE	2B**
HUTH S.	**1C	2B**
PRADHAN C.	**1E	2B**
DIETERICH M.	**1B	2B**
BRANDT T.	**1ABF	2B**
JAHN K.	**1ABF	2B**

1 RESEARCH PROJECT: **A** CONCEPTION | **B** ORGANIZATION | **C** EXECUTION | **D** PROGRAMMING OF DATA ANALYSIS PROCEDURES | **E** DATA ANALYSIS | **F** DATA INTERPRETATION

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2.9 NONLINEAR VARIABILITY OF BODY SWAY IN PATIENTS WITH PHOBIC POSTURAL VERTIGO

SCHNIEPP R*, WUEHR M*, PRADHAN C, NOVOZHILOV S, KRAFCZYK S, BRANDT T, JAHN K

* equal contribution

CONTRIBUTORSHIP

SCHNIEPP R.	**1ABEF | 2A**
WUEHR M.	**1ABDEF | 2A**
PRADHAN C.	**1F | 2B**
NOVOZHILOV S.	**1C | 2B**
KRAFCZYK S.	**1C | 2B**
BRANDT T.	**1ABF | 2B**
JAHN K.	**1ABF | 2B**

1 RESEARCH PROJECT: **A** CONCEPTION | **B** ORGANIZATION | **C** EXECUTION | **D** PROGRAMMING OF DATA ANALYSIS PROCEDURES | **E** DATA ANALYSIS | **F** DATA INTERPRETATION

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2.10 INADEQUATE INTERACTION BETWEEN OPEN- AND CLOSED-LOOP POSTURAL CONTROL IN PHOBIC POSTURAL VERTIGO

WUEHR M, PRADHAN C, NOVOZHILOV S, KRAFCZYK S, BRANDT T, JAHN K, SCHNIEPP R

CONTRIBUTORSHIP

WUEHR M.	**1ABDEF	2A**
PRADHAN C.	**1F	2B**
NOVOZHILOV S.	**1C	2B**
KRAFCZYK S.	**1C	2B**
BRANDT T.	**1ABF	2B**
JAHN K.	**1ABF	2B**
SCHNIEPP R.	**1ABF	2B**

1 RESEARCH PROJECT: **A** CONCEPTION | **B** ORGANIZATION | **C** EXECUTION | **D** PROGRAMMING OF DATA ANALYSIS PROCEDURES | **E** DATA ANALYSIS | **F** DATA INTERPRETATION

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2.11 BALANCE CONTROL AND ANTI-GRAVITY MUSCLE ACTIVITY DURING THE EXPERIENCE OF FEAR AT HEIGHTS

WUEHR M, KUGLER G, SCHNIEPP R, ECKL M, PRADHAN C, JAHN K, HUPPERT D, BRANDT T

CONTRIBUTORSHIP

WUEHR M.	**1ABCDEF | 2A**
KUGLER G.	**1ABCF | 2B**
SCHNIEPP R.	**1ABCF | 2B**
ECKL M.	**1BC**
PRADHAN C.	**1BC**
JAHN K.	**1F | 2B**
HUPPERT D.	**1ABF | 2B**
BRANDT T.	**1ABF | 2B**

1 RESEARCH PROJECT: **A** CONCEPTION | **B** ORGANIZATION | **C** EXECUTION | **D** PROGRAMMING OF DATA ANALYSIS PROCEDURES | **E** DATA ANALYSIS | **F** DATA INTERPRETATION

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3 Discussion

In the following section, the key findings of the studies presented in the previous chapters will be discussed with respect to their functional relevance for sensorimotor postural stability control during standing and walking as well as regarding their clinical implications.

3.1 STABILITY CONTROL DURING LOCOMOTION

3.1.1 *Gait fluctuations and stability control in healthy walkers*

The healthy human walking pattern is characterized by highly complex dynamics that result from the interaction of active sensory and passive biomechanical regulatory processes operating on multiple time scales. Consequently, temporospatial gait cycle parameters not only exhibit stride-to-stride fluctuations but also comprise complex fractal-like long-range correlations, i.e., fluctuations at any arbitrary point of time are statistically related to fluctuations at other time points (Hausdorff, 2005, Hausdorff et al., 1996, Terrier et al., 2005). The amplitude of stride-to-stride fluctuations is commonly referred to as gait variability magnitude, whereas the long-range correlations within the stride-to-stride fluctuations are referred to as the structure of gait variability. From a dynamic systems theory perspective, both of these characteristics of the stride-to-stride fluctuations in the walking pattern can be regarded as relevant markers for the degree of dynamic gait stability. Accordingly it could be demonstrated that increased variability magnitudes and a breakdown of variability structure are associated with increased risk of falls (Herman et al., 2005, Maki, 1997).

Dynamic systems theory furthermore supposes that the characteristics of these gait fluctuations depend on the control parameter, i.e., walking velocity, and exhibit alterations when the control parameter is scaled up or down (Haken, 1977, Kelso, 1995). The studies presented in chapters 2.1 – 2.5 confirm this supposition by demonstrating the speed dependency of gait variability magnitude and structure. They further reveal that the speed dependency of gait variability is differentially regulated for the medio-lateral walking plane (i.e., base width) and the fore-aft walking plane

(i.e., stride time and stride length) (Schniepp et al., 2012b, Wuehr et al., 2013b, Wuehr et al., 2013c, Wuehr et al., 2014b, Wuehr et al., 2014c). Different control strategies apparently underlie each of these directions. Accordingly, we could show that stride-to-stride fluctuations in the medio-lateral walking plane are characterized by large variability magnitudes that even increase for faster walking speeds due to a decrease of the BoS with faster walking modes. The structure of medio-lateral gait fluctuations featured low fractal dimensionality close to a random-like white noise process. Walking adjustments in the medio-lateral direction are thought to be actively controlled by integrative sensory feedback because the passive dynamics of walking appear to be quite unstable in this direction (Bauby and Kuo, 2000, O'Connor and Kuo, 2009). The observed large variability magnitudes and the absence of long-range correlations within the medio-lateral stride-to-stride fluctuations confirm this hypothesis. Thus, these findings indicate that the dynamic stabilization of the medio-lateral walking plane is governed by the active control mode of reactive tuning that acts on short-term time scales, thereby evoking single-frequency responses to restore the stability of the walking subject (Lipsitz, 2002).

In the fore-aft walking plane, both the magnitude and the structure of temporospatial gait fluctuations were shown to exhibit a curvilinear dependency on walking speed with minimal levels of gait variability magnitude and structure at the velocity of self-paced walking in accordance with previous studies (Jordan et al., 2007, Yamasaki et al., 1991, Yamasaki et al., 1984). Increasing levels of gait variability magnitude and structure at slow and fast walking speeds most likely reflect critical fluctuations as an early warning signal of non-equilibrium phase transitions (Haken, 1977, Scheffer et al., 2009). Thus, enhanced instabilities in walking control occur when the walking velocity is close to the walk-run or walk-stand transition. In contrast, minimal levels of gait variability and structure at preferred walking speed are thought to reflect the attractor dynamics of the locomotor system (Jordan et al., 2007). Preferred walking speed, as it is related to the eigenfrequency of the leg, has been supposed to be the most stable walking mode, featuring lowest energy consumption and symmetry of ground reaction forces (Breit and Whalen, 1997, Holt et al., 1990, Holt et al., 1995, Jordan et al., 2007, Zarrugh et al., 1974). The obvious reduction of temporospatial long-range correlations in the walking pattern at preferred speed has been suggested to reflect, on the one hand,

the larger number of degrees of freedom that constrain the locomotor system at the preferred walking mode and to indicate, on the other, an enhanced stability in terms of a higher flexibility and adaptability (Jordan et al., 2007).

The attractor dynamics of the locomotor system were further explored in greater detail by evaluating the fluctuation dynamics in the relative phase between the legs. Human locomotion is based on coordinated rhythmic activity, in which the legs function as two weakly coupled oscillators (Beek et al., 1995). Accordingly, within the framework of dynamic pattern theory it was hypothesized that the relative phase between the two oscillating legs serves as an order parameter of the locomotor system and that the fluctuations within this order parameter represent the attractor dynamics of gait (Schöner et al., 1990). By evaluating the phase synchronization dynamics between the legs over the whole speed spectrum of walking, we were able to confirm this hypothesis (Wuehr et al., 2014b). Phase synchronization between the two oscillating legs was most consistent during preferred walking and exhibited critical fluctuations at the speed boundaries of walking behavior. Enhanced inter-leg phase-synchronization has been shown to be directly linked to gait stability by implying shorter recovery times from external destabilizing perturbations of the walking pattern (Krasovsky et al., 2012, Krasovsky et al., 2013). Thus, an increasing variance in the relative phase between the two oscillating legs at increasingly non-preferred walking speeds indicates slower recovery dynamics from perturbations, which represents another early warning signal of non-equilibrium phase transitions (Haken, 1977, Scheffer et al., 2009). Furthermore, at the transition from walking to running mode the occurrence of a qualitative reorganization of inter-leg phasing as well as a sudden jump in relative phase could be demonstrated, which represent two hallmarks of a non-equilibrium phase transition (Diedrich and Warren Jr, 1995).

In summary, both single- and inter-leg gait dynamics were investigated over the whole velocity spectrum of walking to disclose patterns of optimization within and between these dynamics. Thereby it was demonstrated that the attractor state of preferred walking is characterized by minimal single-leg variability magnitude and structure as well as a most consistent inter-leg phase relationship. Moreover, it was found that the amount of long-range correlations in single-leg

dynamics and the amount of inter-leg phase synchronization are significantly interrelated (Wuehr et al., 2014b). A decrease in single-leg long-range correlations entailed an increase in inter-leg phase synchronization. It has been demonstrated both theoretically and experimentally that less correlated noise, externally imposed on two weakly coupled oscillators, increases the phase synchronization between them, whereas strongly correlated noise suppresses it (Bartsch et al., 2007a, Kiss et al., 2003, Zhou et al., 2002). Thus, single-leg and inter-leg dynamics are likely to exhibit a collective pattern of optimization at the attractor of preferred walking speed. Less correlated noise in the single-leg dynamics at self-paced walking, imposed on the two coupled oscillating legs, increases the phase synchronization between the legs and thereby enhances gait stability at the attractor state of walking. The observed inverse pairing of correlation and synchronization in gait dynamics might in fact be a more general characteristic of physiological systems under neuronal regulation. Accordingly, it was shown that increased cardio-respiratory phase synchronization occurs during deep sleep, when long-range correlations in the cardiac and respiratory dynamics are weakest (Bartsch et al., 2012).

3.1.2 *Sensory feedback control of gait stability*

It is well established that sensory signals contribute to shaping the locomotor pattern and adapting it to environmental demands (Büschges and El Manira, 1998). Sensory feedback control is thought to be particularly important for adjusting stride-to-stride trajectories in order to maintain balance and for smoothing unintended irregularities during walking (Gandevia and Burke, 1992, Nashner, 1980) and should therefore have a greater influence on the stride-to-stride fluctuations within the gait pattern than on the mean temporospatial characteristics of walking (Dingwell et al., 2000). It has been further hypothesized that a disturbance of sensory feedback control might alter the inherent complexity of the walking dynamics to a less complex response mode of reactive tuning, which operates over relatively short time periods to restore the stability of the walking subject (Lauk et al., 1998, Lipsitz, 2002). The studies presented in chapters 2.2–2.4 address these hypotheses by examining the influence of (1) absent visual feedback control (in blindfolded healthy individuals), (2) deficient proprioceptive feedback control (in patients with peripheral neuropathy),

as well as (3) deficient vestibular feedback control (in patients with bilateral vestibular failure) on stability control during walking.

Deficient sensory feedback control of locomotion is known to affect multiple characteristics of the walking kinematics including stride time, stride length, base width, and double support duration (Allet et al., 2008, Hallemans et al., 2009, Ishikawa et al., 1993). However, it could be demonstrated that these apparent alterations in the mean temporospatial characteristics of the walking pattern are due to a slowing down of walking speed under deficient sensory feedback control and cannot be directly attributed to sensory loss itself (Hallemans et al., 2009, Wuehr et al., 2014c). In contrast, we showed that sensory feedback control has a direct effect on the stride-to-stride fluctuations in the walking pattern. This effect is comparable for the different sensory modalities (i.e., visual, proprioceptive, and vestibular) and is differentially pronounced for fluctuations in the medio-lateral and the fore-aft walking directions. Observations in healthy subjects suggest that stability control of gait in the medio-lateral walking plane is governed by a control mode of reactive tuning, which is characterized by the active stabilization of walking based on sensory feedback mechanisms (Bauby and Kuo, 2000, Wuehr et al., 2013c). Moreover, the dominance of this control mode for medio-lateral gait stabilization does not depend on the actual walking speed (Wuehr et al., 2013c). Correspondingly, active stabilization in the medio-lateral plane should be highly sensitive to defects in sensory feedback control. The studies presented in chapters 2.2 and 2.3 confirm this assumption by showing that deficiencies in visual and proprioceptive feedback control lead to a general increase in the magnitude of medio-lateral gait variability at all walking speeds (Wuehr et al., 2013c, Wuehr et al., 2014c). An increase of medio-lateral gait variability has been associated with a decline in dynamic gait stability and a higher risk of falls (Brach et al., 2005, Owings and Grabiner, 2004).

Stabilization in the fore-aft walking plane has been proposed to be established primarily by passive biomechanical regulatory processes and should be therefore essentially independent of high-level neural feedback control (Bauby and Kuo, 2000, Gates et al., 2007, Mcgeer, 1990). Consequently, the regulation of fore-aft gait variability should be rather insensitive to perturbations or deficiencies

in the active sensory feedback control. However, the studies presented in chapters 2.2–2.4 could demonstrate that deficiencies in sensory feedback control of locomotion have a direct effect on gait stabilization in the fore-aft walking plane. Disturbances in either visual, proprioceptive, or vestibular feedback control consistently led to an increase in the magnitude and a decrease in the structure of fore-aft gait variability, thus indicating explicit involvement of active sensory control mechanisms that stabilize gait in the fore-aft plane (Schniepp et al., 2012b, Wuehr et al., 2013c, Wuehr et al., 2014c). Furthermore, fore-aft gait stabilization was even more affected if more than one sensory modality was disturbed during locomotion (Wuehr et al., 2014c).

The effect of deficient sensory feedback control on fore-aft stride-to-stride fluctuations differed considerably for different walking speeds; while major changes occurred at slow walking, the effect diminished at preferred and fast gait speeds. This speed-dependent impact of sensory feedback information on the fore-aft gait variability supports the hypothesis of a speed-dependent sensory locomotor control in the fore-aft walking plane. Accordingly, active sensory feedback control is necessary for balance control mainly during slow locomotion, whereas fast locomotion is thought to be primarily achieved by highly automated central pattern generators in the spinal cord (Brandt et al., 1999, Brandt, 2000, Jahn et al., 2000, Jahn et al., 2001). In agreement with this model, motor imagery studies with fMRI could demonstrate that activations of sensory cortex areas decrease during running and fast walking (Jahn et al., 2004, Jahn et al., 2008a).

Walking instabilities and a higher risk of falls are common in patients suffering from deficient feedback control of one or more sensory modalities (Lord, 2006, Richardson et al., 1992, Whitney et al., 2000). Moreover, the relationship between increased fore-aft gait variability and an increased risk of falls is well established (Guimaraes and Isaacs, 1980, Hausdorff, 2005, Maki, 1997). We further demonstrated that the fore-aft gait variability levels of patients with peripheral neuropathy during walking slowly and walking with eyes closed were the only gait characteristics that showed a significant association with their history of falls (Wuehr et al., 2014c).

3.1.3 *Cerebellar control of gait stability*

The cerebellum is involved in gait control: it functions as an important relay region for the integration of multi-sensory information into the locomotor network and further provides rhythmic input for the coordination of the walking pattern (Mori et al., 1999, Mori et al., 2001). Cerebellar damage has been shown to result, on the one hand, in a poor accuracy of the walking movements (i.e., increased step width, variable foot displacement, irregular foot trajectories, and a stumbling walking path) commonly referred to as ataxic gait (Ilg and Timmann, 2013, Morton and Bastian, 2004), and on the other, in an increased gait variability and a high risk of falling (Fonteyn et al., 2010, Ilg et al., 2007, Ilg et al., 2008). However, the specific influence of the cerebellar locomotor function on the regulation of temporospatial stride-to-stride fluctuations and the control of dynamic gait stability has so far not been elucidated in detail. The studies presented in chapters 2.4–2.8 address this topic, in particular by aiming to clarify how cerebellar locomotor function contributes to gait stabilization and whether this contribution is dependent on the walking speed.

Observations in healthy walkers revealed that gait stabilization is differentially regulated in the medio-lateral and fore-aft walking planes (Bauby and Kuo, 2000, Wuehr et al., 2013c). Correspondingly, we showed that cerebellar dysfunction has a different impact on the stride-to-stride fluctuations in both walking planes. Deficient cerebellar locomotor control led to a decrease of medio-lateral variability structure at all walking speeds (Wuehr et al., 2013b). Since walking adjustments in the medio-lateral direction are thought to be actively controlled by integrative sensory feedback, this observation most likely reflects the impaired sensory integration function of the cerebellum (Walter et al., 2006). The observed alterations in medio-lateral variability have also been linked to an increased risk of falls (Brach et al., 2005, Owings and Grabiner, 2004).

In the fore-aft walking plane, cerebellar dysfunction led to both an increase of gait variability magnitude and a decrease of gait variability structure (Schniepp et al., 2012b, Wuehr et al., 2013b). This effect was dependent on the walking speed, mostly affecting the walking pattern during slow and fast locomotion, whereas the preferred walking mode remained unimpaired. The twofold effect of cerebellar dysfunction on gait variability at slow and fast walking can be interpreted to reflect

two different aspects of cerebellar locomotor control. Accordingly, gait variability alterations during slow walking might reflect impaired sensory integration of cerebellar locomotor regions. Purkinje cells, which are the sole output of the computational circuitry of the cerebellar cortex, supply in their firing rate and pattern of activity the signals required for the execution and coordination of rhythmic walking movements (Ito, 1984, Walter et al., 2006). In the absence of synaptic input, the intrinsically driven pacemaking of Purkinje cells has been shown to be very regular (Womack and Khodakhah, 2002). The spontaneous activity of these cells is shaped by time-variant sensory information relayed over numerous synaptic inputs (Häusser and Clark, 1997). It could be demonstrated in the animal model that decreased precision of the intrinsic pacemaking in Purkinje cells due to cerebellar damage leads to impaired integration of sensory information within the cerebellum and consequently to a more variable motor output (Walter et al., 2006). According to the concept of a speed-dependent sensory integration into the locomotor network (Brandt et al., 1999, Brandt, 2000, Jahn et al., 2000, Jahn et al., 2001), disturbed sensory integration within the cerebellum should affect the dynamics of stride-to-stride fluctuations predominantly during slow walking in agreement with the experimental observations. In contrast, alterations in gait variability during fast walking might reflect impaired cerebellar pacemaker function. In the animal model it could be shown that a loss in precision of the intrinsic pacemaking activity of cerebellar Purkinje cells results in impaired cerebellar locomotor function and a more variable motor output (De Zeeuw et al., 2011, Walter et al., 2006). Moreover, the cerebellar pacemaker region demonstrates enhanced activity with increasing gait speed (Jahn et al., 2008a). Consequently, impaired cerebellar pacemaker function should influence the dynamics of stride-to-stride fluctuations predominantly during fast walking. This again is consistent with the experimental observations.

The assumption that cerebellar Purkinje cell function is directly involved in the regulation of gait variability is further supported by evidence of a case study (chapter 2.6) on two individuals with cerebellar ataxia caused by mutations in the gene CACNA 1A encoding the $Ca_V2.1\,\alpha\,1$ subunit of the P/Q-type voltage-gated calcium channel (Schniepp et al., 2011). These mutations have been shown to result in an overall reduction in the P/Q-type calcium current (Fletcher et al., 1996). A consequence of this reduction in the P/Q calcium current is a loss of precision of pacemaking

activity in cerebellar Purkinje cells (Walter et al., 2006). Alterations in stride-to-stride fluctuations typical for cerebellar patients could be observed in both individuals: their gait variability magnitudes were pathologically increased, predominantly for slow and fast walking speeds. Both subjects were treated with 4-Aminopyridine (4-AP), a reversible potassium channel blocker. 4-AP has been shown to reduce the frequency and severity of attacks in episodic ataxia type 2 (Löhle et al., 2008, Strupp et al., 2004) and to suppress downbeat nystagmus in cerebellar patients (Kalla et al., 2007). In the animal model, 4-AP was shown to restore diminished precision of pacemaking in cerebellar Purkinje cells by prolonging the action potential and increasing the action potential afterhyperpolarization (Alviña and Khodakhah, 2010). Accordingly, treatment with 4-AP led to a considerable decrease of gait variability magnitude at slow walking speeds and an even greater decrease at fast walking modes in both subjects, presumably due to a restoration of pacemaking precision in cerebellar Purkinje cells. Furthermore, in both subjects, treatment with 4-AP resulted in a reduced subjective fall risk, measured by the Falls Efficacy Scale-International (Kempen et al., 2007). The beneficial therapeutic effect of 4-AP on gait variability alterations due to cerebellar dysfunction could be further confirmed in a subsequent case series study (chapter 2.7) of 31 patients with different cerebellar disorders (Schniepp et al., 2012a).

The above-mentioned insights into the characteristic impairments of gait stability control due to cerebellar dysfunction are not only of value for monitoring medical treatment effects but may also promote fall risk estimation procedures. Accordingly, in a fall risk study on cerebellar patients (chapter 2.8) we demonstrated that the amount of fore-aft variability is significantly associated with the fall history of patients. This finding even allowed us to discriminate between occasional and frequent fallers (Schniepp et al., 2014b).

Finally, the observed effect of cerebellar dysfunction on the structure of gait variability supports the supposition that long-range correlations within the stride-to-stride fluctuations of the walking pattern do not solely have a biomechanical origin (Gates et al., 2007), but more likely arise from the interference of higher neural and biomechanical oscillatory dynamics (Hausdorff et al., 1995, Hausdorff et al., 1997).

3.1.4 *Conclusions and directions for further research*

Dynamic gait stability depends on the walking speed and is differentially regulated in the medio-lateral and fore-aft walking planes. Studying the fluctuations of the locomotor system's order parameter (i.e., the fluctuations within the relative phase between the two oscillating legs) allows us to disclose the attractor dynamics of the walking mode. Accordingly, gait at preferred velocity is characterized by minimal fluctuations in the order parameter and thus represents the attractor state of the walking mode. If the control parameter of gait (i.e., the walking velocity) is scaled up or down, the dynamics of the order parameter exhibit critical fluctuations, indicating that walking at increasingly non-preferred gait speeds implies a decline in dynamic gait stability.

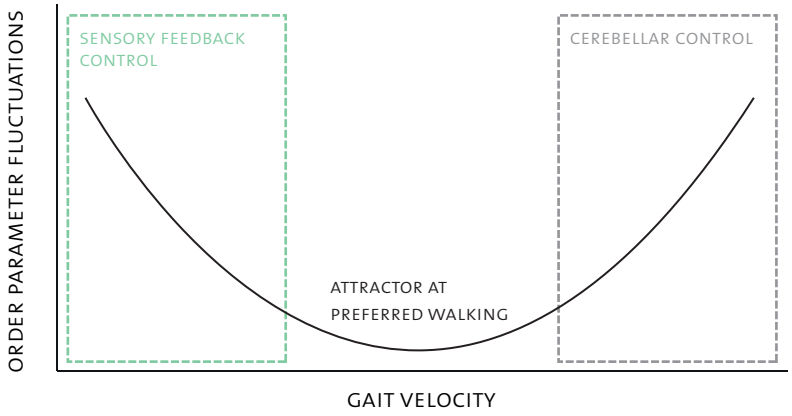

Figure 5 Speed-dependent control of gait stability. The stability of the walking pattern is reflected in the fluctuations of the order parameter of the locomotor system, i.e., the fluctuations within the relative phase between the two oscillating legs. The stability conditions of the locomotor system alter if the control parameter (i.e., gait velocity) is scaled up or down. Accordingly, preferred walking speed represents the attractor state of walking behavior with minimal fluctuations in the order parameter. At increasingly non-preferred walking speeds, critical fluctuations in the order parameter occur which reflect a loss of dynamic gait stability close to the speed boundaries of the walking mode. The regulation of gait fluctuations during slow walking speeds is critically dependent on sensory feedback control, whereas gait fluctuations during fast walking are mainly regulated by cerebellar locomotor regions. The pattern of optimization at preferred walking speed is essentially independent of active sensory feedback or cerebellar locomotor control and presumably arises from passive biomechanical tuning mechanisms.

The regulation of gait fluctuations during slow walking is critically dependent on sensory feedback control. Accordingly, a disturbance in the operation of sensory feedback mechanisms (either due to false or absent sensory input or due to deficient supraspinal sensory integration) results in a critical rise of stride-to-stride fluctuations, predominantly during slow locomotion speeds. In contrast, the regulation of gait fluctuation during fast walking relies on the smooth operation

of cerebellar locomotor control. Deficient cerebellar pacemaker function correspondingly results in critically increased stride-to-stride fluctuations primarily during fast locomotion speeds. Critically increased gait fluctuations due to deficient sensory or cerebellar locomotor control involve a decline of dynamic gait stability, which is indicated by an increased risk of falls. Furthermore, disturbances in either sensory or cerebellar locomotor control do not appear to influence the attractor dynamics at self-paced walking, suggesting that the apparent pattern of optimization at preferred walking speed emerges from passive biomechanical tuning mechanisms. (Figure 5)

The studies presented here examined dynamic gait stability exclusively during the performance of steady-state locomotion. To gain a more comprehensive understanding of the control mechanisms and the conditions of dynamic gait stability, complementary studies are required that evaluate stability control of walking during disequilibrium states. Postural disequilibrium states may be induced internally by the performance of complex postural maneuvers (i.e., turns, changes in walking direction, etc.) or triggered externally by targeted mechanical perturbations of the steady-state walking condition. Experiments including targeted perturbations of the steady-state walking condition would allow an evaluation of the recovery dynamics of the walking system. A system's recovery rate after small perturbation has been shown to reflect the degree of the system's overall stability. Consequently, besides critical order parameter fluctuations, slower recovery dynamics from perturbations represent an essential early warning signal of a non-equilibrium phase transition (Haken, 1977, Scheffer et al., 2009). So far, experimental setups including targeted perturbations of the steady-state walking condition were limited to the examination of only one gait speed, thereby neglecting the attractor dynamics of walking (Krasovsky et al., 2012, Krasovsky et al., 2013). Future studies should therefore address both the influence of walking speed as well as the impact of disturbed sensory or supraspinal locomotor control on the recovery dynamics of walking.

3.2 POSTURAL CONTROL IN CONDITIONS OF SUBJECTIVE IMBALANCE AND VERTIGO

3.2.1 *Postural control in phobic postural vertigo*

The syndrome of phobic postural vertigo (PPV) is characterized by subjective dizziness and a disturbance of balance while standing and walking, despite normal values in clinical balance tests (Brandt, 1996). PPV – also termed visual vertigo syndrome (Bronstein, 1995) or chronic subjective dizziness (Staab and Ruckenstein, 2007) – is one of the primary and secondary somatoform dizziness syndromes (Best et al., 2006, Eckhardt-Henn et al., 2003, Furman and Jacob, 1997). As one of the most frequent causes of chronic dizziness, it has a high impact on functioning and quality of life (Best et al., 2006).

Stable balance control during standing requires the continuous evaluation of reafferent sensory feedback of self-generated body movements (Morasso et al., 1999). Inadequate compensation for self-induced sensory stimulation, which triggers the perception of motion illusions due to self-motion, has been hypothesized to be the mechanism underlying subjective vertigo in PPV (Brandt and Dieterich, 1986, Brandt, 1996). According to this hypothesis, self-motion-induced reafferent sensory stimulation would be wrongly perceived as motion in the environment. This would happen because the predictive efference copy signal reflecting the consequences of self-generated body movements, necessary to compensate for the reafferent stimulus, is inappropriate (Pomper et al., 2013). The mismatch between anticipated and actual motion perception has been further hypothesized to be caused by an inadequate postural control strategy, which implies anxious controlling of balance regulation and the conscious perception of sensorimotor adjustments that would normally be accomplished unconsciously (Brandt, 1996).

Previous studies reported first evidence for the presence of an inadequate postural control scheme in PPV, e.g., an increase in muscle expenditure and high-frequency body sway (Holmberg et al., 2003, Krafczyk et al., 1999). Such postural control alterations are comparable to that observed in healthy subjects when confronted with a demanding balance situation, such as standing on a high platform (Carpenter et al., 2001). Furthermore, during the performance of a complex balance task,

such as tandem stance on foam rubber with eyes closed, the postural behavior of patients with PPV assimilated to that of healthy persons standing under the same condition (Querner et al., 2000). These findings indicate that subjective imbalance in PPV is caused by the application of an inappropriate balance strategy due to anxious control of posture (Holmberg et al., 2005, Tjernstrom et al., 2009). The purpose of the studies presented in chapters 2.9 and 2.10 was to further elucidate and characterize the sensorimotor mechanisms underlying inadequate postural control in PPV.

The study presented in chapter 2.9 characterized postural performance in PPV by evaluating, on the one hand, the structure of body sway variability, i.e., the strength of long-range correlations within the CoP time series, and on the other, the regularity of the CoP time series by means of a sample entropy analysis (Lake et al., 2002, Richman and Moorman, 2000). Healthy balance performance under normal stance conditions is known to exhibit highly irregular, complex dynamics representing the interaction of regulatory processes, which operate on different time scales (Donker et al., 2007). Such processes are thought to enable the postural control system to prepare postural responses to sudden balancing stresses and to thereby enhance the overall stability of a standing subject (Lipsitz, 2002). In contrast, we showed that postural control in patients with PPV under normal balance conditions is characterized by a less complex, i.e., more constrained and regular mode of standing compared to that of healthy subjects (Schniepp et al., 2013). Patients with PPV exhibited an increase in strength of long-range correlations within the CoP time series. The stronger dependency between different time scales within the CoP signal indicates a decrease in the number of independently controllable system elements contributing to the motor output. This results in a more constrained mode of postural control with decreased dynamic stability (Jordan et al., 2007, Slifkin and Newell, 1999). Furthermore, the postural performance of patients with PPV featured an increase in regularity within the CoP time series. Decreased complexity in terms of a more regular sway pattern indicates that the postural behavior is more rigid within repeating patterns, thereby losing adaptability and dynamic stability (Borg and Laxåback, 2010).

Previous studies provided evidence for a close connection between the regularity of CoP displacements and the amount of attention invested in postural control (Donker et al., 2007). Consequently,

increased regularity within the sway pattern of patients with PPV suggests that inadequate balance performance in PPV is caused by a shift to a more attentional mode of postural control. This supposition is further supported by the observation that the less complex sway pattern of patients with PPV while standing under normal balance conditions resembles the sway pattern of healthy subjects while performing a more complex, attention-demanding balance task (Donker et al., 2007, Duarte and Sternad, 2008, Schniepp et al., 2013). In conformance with previous observations, we further demonstrated that during the performance of such complex, attention-demanding balance tasks the postural behavior of patients with PPV assimilates to that of healthy subjects performing the same task (Querner et al., 2000). Taken together, these observations support the hypothesis that patients with PPV apply at baseline a postural control strategy governed by exaggerated attentional involvement that is used in the healthy mode only for the most demanding balance tasks. In accordance with this hypothesis, we showed that walking of patients with PPV is associated with increased attentional demands and features the typical characteristics of a cautious gait (Schniepp et al., 2014a).

The study presented in chapter 2.10 further examined inadequate postural behavior in PPV within the framework of SDA (Collins and De Luca, 1993b), in order to determine the characteristics and modes of interaction of open- and closed-loop processes that make up the postural control scheme in PPV. It was found that patients with PPV exhibit a considerable increase in their steady-state behavior of open-loop postural control, while normal closed-loop activity (Wuehr et al., 2013a). Increased open-loop activity has been associated with an increase in stiffness and a decrease of damping of the postural control system (Collins et al., 1995, Collins and De Luca, 1993b, Peterka, 2000). Accordingly, this finding suggests a stiffening of the musculoskeletal system due to increased muscular activity across the joints of the lower limbs. It is known that the force output of skeletal muscles contains noise-like fluctuations (De Luca et al., 1982) that increase with muscle activity (Galganski et al., 1993). Larger noise-like fluctuations over joints caused by increased levels of muscle activity would therefore lead to amplified short-term postural sway which reflects the amount of open-loop activity in the postural control scheme. Correspondingly, it could be shown that the extent of open-loop activity and the amount of anti-gravity muscle co-contraction

are positively correlated (Laughton et al., 2003). This line of interpretation is consistent with the hypothesis that inadequate postural performance in patients with PPV might be caused by an increase in co-contraction of anti-gravity muscles (Krafczyk et al., 1999, Querner et al., 2000) – a pattern of muscle activation that is applied by healthy subjects only if they consciously concentrate on balance control, i.e., when learning a new motor task or when uncertainty exists about a required task (De Luca and Mambrito, 1987, Smith, 1981).

Furthermore, balance behavior in patients with PPV featured a precipitate transition behavior from the open- to the closed-loop control mode (Wuehr et al., 2013a). The critical point of transition between the two control modes has been associated with the first-level stability limit of the postural control system, i.e., its primary feedback threshold (Collins and De Luca, 1993b). An earlier transition significantly shortens the effective range of the steady-state open-loop regime and thereby lowers the primary sensory feedback threshold of the postural control scheme. In healthy subjects, the complexity of the stochastic open-loop steady-state behavior enables the postural control system to flexibly adapt closed-loop responses to sudden balancing stresses. In contrast, limited open-loop control in patients with PPV triggers precipitate integration of sensory feedback into the postural control scheme, which may lead to maladaptive responses to external perturbations. Such shortcomings in closed-loop sensory feedback control could also be responsible for a mismatch between anticipated and actual motion perception, which has been hypothesized to underlie subjective vertigo in PPV (Brandt and Dieterich, 1986, Brandt, 1996).

Altogether, these findings suggest that PPV does not involve a functional disturbance of the postural control system. However, the open- and closed-loop control system as a whole appears to be not optimally tuned in patients with PPV. The control systems are working but in an inadequate way, with the result that they are not as smoothly and efficiently functioning as in healthy subjects. This inadequately tuned balance regulation might further elicit the experience of subjective imbalance and vertigo in patients with PPV.

3.2.2 *Postural control in visual height intolerance*

Visual stimulation of heights is known to provoke individual responses that vary on a continuum from physiological visual height imbalance to acrophobia, the severest end of the spectrum (Brandt and Huppert, 2014, Salassa and Zapala, 2009). The common response experienced by everyone is a physiological visual height imbalance that results from a mismatch between visual distance cues and the perception of self-movement, when the distance between eyes and nearest objects in the environment reaches a certain threshold (Brandt et al., 1980, Salassa and Zapala, 2009). Acrophobia is defined to be a specific phobia, implying that an anticipatory fear leads to avoidance of heights (Clarke, 1995). In-between the common physiological and the phobic reaction to heights, there is a stimulus-dependent visual height intolerance (vHI), which causes the apprehension of losing balance or falling, but does not meet the diagnostic criteria of a specific phobia (Brandt et al., 2012, Brandt and Huppert, 2014). VHI has been shown to affect almost one third of the general population (Huppert et al., 2013). Individuals susceptible to vHI experience subjective postural imbalance with to-and-fro vertigo when confronted with a height stimulus. The study presented in chapter 2.11 explored alterations in postural control and anti-gravity muscle activity that trigger subjective vertigo in subjects susceptible to vHI during height exposure. Furthermore, the specific influences of visual stimulation and attention on altered postural performance in vHI were determined.

While standing at heights, susceptible individuals exhibited alterations in their postural control scheme that clearly resembled those observed in patients with PPV, namely (1) an increased steady-state activity of open-loop control, and (2) a lowered threshold for sensory feedback integration into the postural control regime (Wuehr et al., 2014a). These alterations in postural control were further linked to specific changes in muscle innervation patterns, in particular an enhanced co-contraction of anti-gravity leg and neck muscles. The observed stiffening of the neck musculature agrees with the previously reported reduction of spontaneous head movement in subjects susceptible to vHI during height exposure (Kugler et al., 2013). Changes in leg muscle activation during height threat might partly result from a leaning away from the edge (Carpenter et al., 2001, Pasman et al., 2011). An increased stiffness and immobilization of the musculoskeletal system, as exhibited by

susceptible individuals while standing at heights, has been further demonstrated to significantly impair postural equilibrium control during free stance (De Freitas et al., 2009, Gruneberg et al., 2004, Koskimies et al., 1997).

The observed alterations in postural control and accompanying muscle innervation patterns for individuals susceptible to vHI during height exposure were only present when the distance between stationary contrasts in the surrounding and the eyes was critically large. They disappeared when nearby stationary cues in the periphery of the visual field were provided. A critically increased eye-object distance has been shown to result in a mismatch between visual distance cues and the perception of self-movement, which as a consequence triggers postural imbalance – a phenomenon called physiological visual height imbalance (Bles et al., 1980, Brandt et al., 1980). These observations suggest that physiological visual height imbalance triggers postural disequilibrium in vHI. However, altered balance control also diminished when the attentional focus of susceptible individuals was distracted from the height threat, i.e., during the performance of a cognitive dual task. Increased attention to balance regulation indicates an anxious control of posture (Maki and McIlroy, 1996). Moreover, fear at heights appears to not only influence the balance strategy in susceptible individuals but also restricts their visual exploration, which suggests an anxiety-driven visual avoidance behavior (Kugler et al., 2013). Taken together, these findings indicate two distinct sources for postural imbalance in individuals susceptible to vHI: both the critical distance to stationary surroundings in the visual environment and the anxiety evoked by a height threat appear to trigger inadequate balance control in these subjects.

Finally, all observed alterations in balance behavior during height exposure were associated with the subjective estimates of fear experienced by susceptible individuals during height threat. This suggests that the degree of manifestation of altered postural control and the amount of anxiety experienced during height threat are mutually linked in individuals susceptible to vHI, leading to a vicious circle of fear, perception, and postural instability (Schaeffler et al., 2013).

3.2.3 *Conclusions and directions for further research*

The studies presented here reveal a notable conformance of the inadequate mode of balance regulation in individuals suffering from either PPV or vHI. This observation suggests that a general anxiety-driven rather than a height-specific motor reaction may underlie these two distinct forms of subjective imbalance and vertigo. Taken together, the above-discussed findings allow to hypothesize the following circular cascade of symptom emergence in PPV and vHI: (1) An exaggerated conscious concentration on the regulation of postural stability might trigger (2) higher levels of co-contraction in anti-gravity muscles. This stiffening of the musculoskeletal system would in turn lead to (3) the observed inadequate mode of interaction between open- and closed-loop mechanisms within the postural control system, which as a consequence might elicit (4) the experience of subjective imbalance and vertigo. Subjective imbalance in turn would further increase (1) the conscious concentration on balance regulation. (Figure 6)

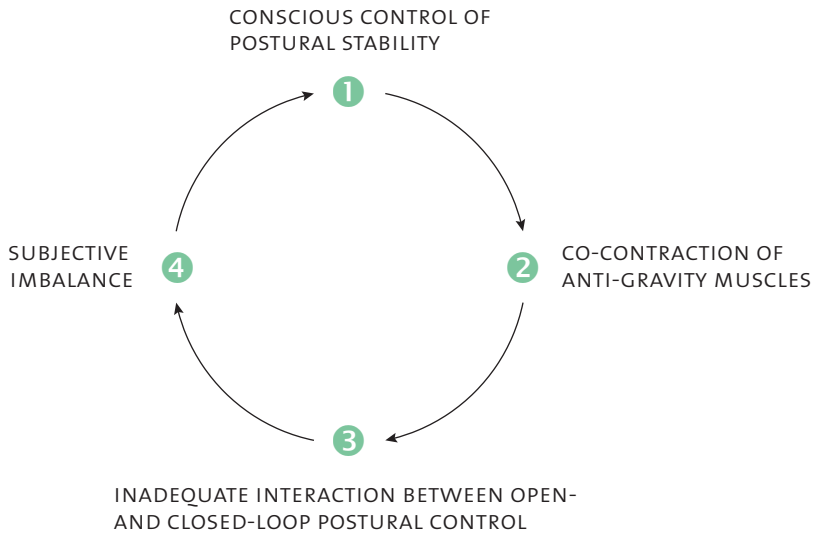

Figure 6 Hypothetical cascade of symptom emergence in PPV and vHI: (**1**) An exaggerated conscious concentration on control of postural stability might trigger (**2**) increased levels of anti-gravity muscle co-contraction. This in turn would lead to (**3**) an inadequate mode of interaction between open- and closed-loop mechanisms within the postural control system that as a consequence might elicit (**4**) the experience of subjective imbalance and vertigo. Subjective imbalance in turn would further enhance (**1**) conscious control of posture.

So far, the hypothesis of enhanced anti-gravity muscle co-contraction has only been verified for the condition of vHI. It remains to be validated for patients with PPV. Furthermore, dual task

examinations are required to directly evaluate the influence of attention and anxiety on the postural performance of patients with PPV, as it has already been accomplished for individuals susceptible to vHI. The studies presented here examined postural equilibrium control in PPV and vHI solely under the steady-state condition of quiet standing. To further elucidate the consequences of altered postural performance in PPV and vHI for the control of dynamic postural stability, complementary studies are needed that assess the quality of postural responses and the course of recovery from momentary states of postural disequilibrium. For this purpose, transient postural destabilization may be either induced internally by the performance of active body movements or triggered externally by mechanical perturbation of the steady-state stance condition. Such experimental setups will also allow validation of the presumed mismatch between anticipated and actual motion perception that has been hypothesized to elicit subjective vertigo in both PPV and vHI.

Bibliography

Allet L, Armand S, Golay A, Monnin D, De Bie R, De Bruin E. Gait characteristics of diabetic patients: a systematic review. *Diabetes Metab Res Rev*. 2008;**24**(3):173-91.

Allum J, Honegger F, Schicks H. The influence of a bilateral peripheral vestibular deficit on postural synergies. *J Vestib Res*. 1993a;**4**(1):49-70.

Allum J, Honegger F, Schicks H. Vestibular and proprioceptive modulation of postural synergies in normal subjects. *J Vestib Res*. 1993b;**3**(1):59-85.

Alviña K, Khodakhah K. The therapeutic mode of action of 4-aminopyridine in cerebellar ataxia. *J Neurosci*. 2010;**30**(21):7258-68.

Angelaki DE, Cullen KE. Vestibular system: the many facets of a multimodal sense. *Annu Rev Neurosci*. 2008;**31**:125-50.

Armstrong D. The supraspinal control of mammalian locomotion. *J Physiol*. 1988;**405**(1):1-37.

Aruin AS, Latash ML. The role of motor action in anticipatory postural adjustments studied with self-induced and externally triggered perturbations. *Exp Brain Res*. 1995;**106**(2):291-300.

Assaiante C, Marchand A, Amblard B. Discrete visual samples may control locomotor equilibrium and foot positioning in man. *J Mot Behav*. 1989;**21**(1):72-91.

Bardy BG, Marin L, Stoffregen TA, Bootsma RJ. Postural coordination modes considered as emergent phenomena. *J Exp Psychol Hum Percept Perform*. 1999;**25**(5):1284-301.

Bardy B, Oullier O, Bootsma RJ, Stoffregen TA. Dynamics of human postural transitions. *J Exp Psychol Hum Percept Perform*. 2002;**28**(3):499-514.

Bartsch R, Kantelhardt JW, Penzel T, Havlin S. Experimental evidence for phase synchronization transitions in the human cardiorespiratory system. *Phys Rev Lett*. 2007a;**98**(5):54102.

Bartsch R, Plotnik M, Kantelhardt JW, Havlin S, Giladi N, Hausdorff JM. Fluctuation and synchronization of gait intervals and gait force profiles distinguish stages of Parkinson's disease. *Physica A*. 2007b;**383**(2):455-65.

Bartsch RP, Schumann AY, Kantelhardt JW, Penzel T, Ivanov P. Phase transitions in physiologic coupling. *Proc Natl Acad Sci U S A*. 2012;**109**(26):10181-86.

Bauby CE, Kuo AD. Active control of lateral balance in human walking. *J Biomech*. 2000;**33**(11):1433-40.

Beckley D, Bloem B, Remler M. Impaired scaling of long latency postural reflexes in patients with Parkinson's disease. *Electroencephalogr Clin Neurophysiol*. 1993;**89**(1):22-28.

Beek P, Peper C, Stegeman D. Dynamical models of movement coordination. *Hum Mov Sci*. 1995;**14**(4):573-608.

Benda BJ, Riley P, Krebs DE. Biomechanical relationship between center of gravity and center of pressure during standing. *IEEE Trans Rehabil Eng*. 1994;**2**(1):3-10.

Bent LR, Inglis JT, McFadyen BJ. When is vestibular information important during walking? *J Neurophysiol*. 2004;**92**(3):1269-75.

Bernstein NA. The co-ordination and regulation of movements. Pergamon Press, Oxford; 1967.

Berthoz A, Lacour M, Soechting J, Vidal P. The role of vision in the control of posture during linear motion. *Prog Brain Res*. 1979;**50**:197-209.

Best C, Eckhardt-Henn A, Diener G, Bense S, Breuer P, Dieterich M. Interaction of somatoform and vestibular disorders. *J Neurol Neurosurg Psychiatry*. 2006;**77**(5):658-64.

Black FO, Wall III C, Rockette Jr HE, Kitch R. Normal subject postural sway during the Romberg test. *Am J Otolaryngol*. 1982;**3**(5):309-18.

Bles W, Kapteyn TS, Brandt T, Arnold F. The mechanism of physiological height vertigo. II. Posturography. *Acta Otolaryngol*. 1980;**89**(5-6):534-40.

Bloem BR, Beckley DJ, Remler MP, Roos RA, van Dijk JG. Postural reflexes in Parkinson's disease during 'resist'and 'yield'tasks. *J Neurol Sci*. 1995;**129**(2):109-19.

Borg FG, Laxåback G. Entropy of balance- some recent results. *J Neuroeng Rehabil*. 2010;**7**(1):7-38.

Brach JS, Berlin JE, Vanswearingen JM, Newman AB, Studenski SA. Too much or too little step width variability is associated with a fall history in older persons who walk at or near normal gait speed. *J Neuroeng Rehabil*. 2005;**2**(1):2-21.

Brandt T, Wenzel D, Dichgans J. Visual stabilization of free stance in infants: A sign of maturity. *Arch Psychiatr Nervenkr*. 1976;**223**(1):1-13.

Brandt T, Arnold F, Bles W, Kapteyn TS. The mechanism of physiological height vertigo. I. Theoretical approach and psychophysics. *Acta Otolaryngol*. 1980;**89**(5-6):513-23.

Brandt T, Dieterich M. Phobischer Attacken-Schwankschwindel, ein neues Syndrom? *Münch Med Wochenschr*. 1986;**128**:247-50.

Brandt T. Phobic postural vertigo. *Neurology*. 1996;**46**(6):1515-19.

Brandt T, Bartenstein P, Janek A, Dieterich M. Reciprocal inhibitory visual-vestibular interaction. Visual motion stimulation deactivates the parieto-insular vestibular cortex. *Brain*. 1998;**121**(9):1749-58.

Brandt T, Strupp M, Benson J. You are better off running than walking with acute vestibulopathy. *Lancet*. 1999;**354**(9180):746.

Brandt T. Vestibulopathic gait: you're better off running than walking. *Curr Opin Neurol*. 2000;**13**(1):3-5.

Brandt T, Strupp M, Benson J, Dieterich M. Vestibulopathic gait: Walking and running. *Adv Neurol*. 2001;**87**:165-72.

Brandt T, Benson J, Huppert D. What to call "non-phobic" fear of heights. *Br J Psychiatry*. 2012;**190**:81.

Brandt T, Huppert D. Fear of heights and visual height intolerance. *Curr Opin Neurol*. 2014;**27**(1):111-17.

Breit GA, Whalen RT. Prediction of human gait parameters from temporal measures of foot-ground contact. *Med Sci Sports Exerc*. 1997;**29**(4):540-47.

Bronstein AM, Hood JD, Gresty MA, Panagi C. Visual control of balance in cerebellar and parkinsonian syndromes. *Brain*. 1990;**113**(3):767-79.

Bronstein AM. Visual vertigo syndrome: clinical and posturography findings. *J Neurol Neurosurg Psychiatry*. 1995;**59**(5):472-76.

Büschges A, El Manira A. Sensory pathways and their modulation in the control of locomotion. *Curr Opin Neurobiol*. 1998;**8**(6):733-39.

Carpenter MG, Frank JS, Silcher CP, Peysar GW. The influence of postural threat on the control of upright stance. *Exp Brain Res*. 2001;**138**(2):210-18.

Chiel HJ, Ting LH, Ekeberg Ö, Hartmann MJ. The brain in its body: motor control and sensing in a biomechanical context. *J Neurosci*. 2009;**29**(41):12807-14.

Clarke JC. The etiology of acrophobia and its relationship to severity and individual response patterns. *Behav Res Ther*. 1995;**33**(7):795-803.

Collins JJ, Stewart I. Coupled nonlinear oscillators and the symmetries of animal gaits. *J Nonlinear Sci*. 1993a;**3**(1):349-92.

Collins JJ, De Luca CJ. Open-loop and closed-loop control of posture: a random-walk analysis of center-of-pressure trajectories. *Exp Brain Res*. 1993b;**95**(2):308-18.

Collins JJ, De Luca CJ. Random walking during quiet standing. *Phys Rev Lett*. 1994;**73**(5):764-67.

Collins JJ, De Luca CJ, Burrows A, Lipsitz LA. Age-related changes in open-loop and closed-loop postural control mechanisms. *Exp Brain Res*. 1995;**104**(3):480-92.

Corriveau H, Hébert R, Prince F, Raiche M. Postural control in the elderly: an analysis of test-retest and interrater reliability of the COP-COM variable. *Arch Phys Med Rehabi*l. 2001;**82**(1):80-5.

Courtemanche R, Teasdale N, Boucher P, Fleury M, Lajoie Y, Bard C. Gait problems in diabetic neuropathic patients. *Arch Phys Med Rehabil*. 1996;**77**(9):849-55.

Creath R, Kiemel T, Horak FB, Peterka RJ, Jeka JJ. A unified view of quiet and perturbed stance: simultaneous co-existing excitable modes. *Neurosci Lett*. 2005;**377**(2):75-80.

Cromwell RL, Newton RA, Forrest G. Influence of vision on head stabilization strategies in older adults during walking. *J Gerontol A Biol Sci Med Sci*. 2002;**57**(7):442-48.

Davis WJ, Ayers JL. Locomotion: Control by positive-feedback optokinetic responses. *Science*. 1972;**177**(4044):183-85.

De Freitas PB, Freitas SM, Duarte M, Latash ML, Zatsiorsky VM. Effects of joint immobilization on standing balance. *Hum Mov Sci*. 2009;**28**(4):515-28.

De Luca CJ, LeFever RS, McCue MP, Xenakis AP. Control scheme governing concurrently active human motor units during voluntary contractions. *J Physiol*. 1982;**329**:129-42.

De Luca CJ, Mambrito B. Voluntary control of motor units in human antagonist muscles: coactivation and reciprocal activation. *J Neurophysiol*. 1987;**58**(3):525-42.

De Zeeuw CI, Hoebeek FE, Bosman LW, Schonewille M, Witter L, Koekkoek SK. Spatiotemporal firing patterns in the cerebellum. *Nat Rev Neurosci*. 2011;**12**(6):327-44.

Deliagina TG, Orlovsky GN, Zelenin PV, Beloozerova IN. Neural bases of postural control. *Physiology*. 2006;**21**(3):216-25.

Deliagina TG, Zelenin PV, Beloozerova IN, Orlovsky GN. Nervous mechanisms controlling body posture. *Physiol Behav*. 2007; **92**(1):148-54.

Delignieres D, Torre K, Lemoine L. Methodological issues in the application of monofractal analyses in psychological and behavioral research. *Nonlinear Dynamics Psychol Life Sci*. 2005;**9**(4):435-61.

Delignieres D, Torre K, Bernard PL. Transition from persistent to anti-persistent correlations in postural sway indicates velocity-based control. *PLoS Comput Biol*. 2011;7(2):e1001089.

DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci*. 1990;**13**(7):281-85.

Diedrich FJ, Warren Jr WH. Why change gaits? Dynamics of the walk-run transition. *J Exp Psychol Hum Percept Perform*. 1995;**21**(1):183-202.

Diener H, Dichgans J, Guschlbauer B, Mau H. The significance of proprioception on postural stabilization as assessed by ischemia. *Brain Res*. 1984;**296**(1):103-09.

Dietz V. Spinal cord pattern generators for locomotion. *Clin Neurophysiol*. 2003;**114**(8):1379-89.

Dingwell JB, Cusumano JP, Sternad D, Cavanagh PR. Slower speeds in patients with diabetic neuropathy lead to improved local dynamic stability of continuous overground walking. *J Biomech*. 2000;**33**(10):1269-77.

Donker SF, Roerdink M, Greven AJ, Beek PJ. Regularity of center-of-pressure trajectories depends on the amount of attention invested in postural control. *Exp Brain Res*. 2007;**181**(1):1-11.

Drew T, Prentice S, Schepens B. Cortical and brainstem control of locomotion. *Prog Brain Res*. 2004;**143**:251-61.

Duarte M, Sternad D. Complexity of human postural control in young and older adults during prolonged standing. *Exp Brain Res*. 2008;**191**(3):265-76.

Eckhardt-Henn A, Breuer P, Thomalske C, Hoffmann SO, Hopf HC. Anxiety disorders and other psychiatric subgroups in patients complaining of dizziness. *J Anxiety Disord*. 2003;**17**(4):369-88.

Faisal AA, Selen LP, Wolpert DM. Noise in the nervous system. *Nat Rev Neurosci*. 2008;**9**(4):292-303.

Fitzpatrick RC, Burke D, Gandevia SC. Loop gain of reflexes controlling human standing measured with the use of postural and vestibular disturbances. *J Neurophysiol*. 1996;**76**(6):3994-4008.

Fitzpatrick RC, Wardman DL, Taylor JL. Effects of galvanic vestibular stimulation during human walking. *J Physiol*. 1999;**517**(3):931-39.

Fletcher CF, Lutz CM, O'Sullivan TN, Shaughnessy Jr JD, Hawkes R, Frankel WN, Copeland NG, Jenkins NA. Absence epilepsy in tottering mutant mice is associated with calcium channel defects. *Cell*. 1996;**87**(4):607-17.

Fonteyn EM, Schmitz-Hübsch T, Verstappen CC, Baliko L, Bloem BR, Boesch S, Bunn L, Charles P, Dürr A, Filla A. Falls in spinocerebellar ataxias: results of the EuroSCA Fall Study. *Cerebellum*. 2010;**9**(2):232-39.

Forssberg H, Nashner LM. Ontogenetic development of postural control in man: adaptation to altered support and visual conditions during stance. *J Neurosci*. 1982;**2**(5):545-52.

Fossion R, Landa E, Stransky P, Velazquez V, Vieyra JL, Garduno I, Garcia D, Frank A. Scale invariance as a symmetry in physical and biological systems: Listening to photons, bubbles and heartbeats. *AIP Conf Proc*; 2010;**1323**(1):74-90.

Fukuyama H, Ouchi Y, Matsuzaki S, Nagahama Y, Yamauchi H, Ogawa M, Kimura J, Shibasaki H. Brain functional activity during gait in normal subjects: a SPECT study. *Neurosci Lett*. 1997;**228**(3):183-86.

Fung J, Macpherson JM. Attributes of quiet stance in the chronic spinal cat. *J Neurophysiol*. 1999;**82**(6):3056-65.

Furman JM, Jacob RG. Psychiatric dizziness. *Neurology*. 1997;**48**(5):1161-66.

Galganski ME, Fuglevand AJ, Enoka RM. Reduced control of motor output in a human hand muscle of elderly subjects during submaximal contractions. *J Neurophysiol*. 1993;**69**(6):2108-15.

Gandevia SC, Burke D. Does the nervous system depend on kinesthetic information to control natural limb movements? *Behav Brain Sci*. 1992;**15**(4):614-32.

Gates DH, Su JL, Dingwell JB. Possible Biomechanical Origins of the Long-Range Correlations in Stride Intervals of Walking. *Physica A*. 2007;**380**:259-70.

Geursen J, Altena D, Massen C, Verduin M. A model of the standing man for the description of his dynamic behaviour. Agressologie. 1976;**17**:63-69.

Gibson JJ. Visually controlled locomotion and visual orientation in animals. *Br J Psychol*. 1958;**49**(3):182-94.

Gramann K, Gwin JT, Ferris DP, Oie KS, Jung TP, Lin CT, Liao LD, Makeig S. Cognition in action: imaging brain/body dynamics in mobile humans. *Rev Neurosci*. 2011;**22**(6):593-608.

Grillner S, Zangger P. On the central generation of locomotion in the low spinal cat. *Exp Brain Res*. 1979;**34**(2):241-61.

Grillner S, Wallen P. Central pattern generators for locomotion, with special reference to vertebrates. *Annu Rev Neurosci*. 1985;**8**(1):233-61.

Grillner S. The motor infrastructure: from ion channels to neuronal networks. *Nat Rev Neurosci*. 2003;**4**(7):573-86.

Gruneberg C, Bloem BR, Honegger F, Allum JH. The influence of artificially increased hip and trunk stiffness on balance control in man. *Exp Brain Res*. 2004;**157**(4):472-85.

Guimaraes R, Isaacs B. Characteristics of the gait in old people who fall. *Disabil Rehabil*. 1980;**2**(4):177-80.

Gurfinkel V, Levick YS. Perceptual and automatic aspects of the postural body scheme. In: Paillard J, editor. Brain and space. *Oxford University Press*, New York. 1991:147-62.

Gutierrez EM, Helber MD, Dealva D, Ashton-Miller JA, Richardson JK. Mild diabetic neuropathy affects ankle motor function. *Clin Biomech*. 2001;**16**(6):522-28.

Haken H. Synergetics: an introduction : nonequilibrium phase transitions and self-organization in physics, chemistry, and biology. *Springer*, New York. 1977.

Haken H, Kelso J, Bunz H. A theoretical model of phase transitions in human hand movements. *Biol Cybern*. 1985;**51**(5):347-56.

Haken H. Complexity and Complexity Theories: Do These Concepts Make Sense? In: Portugali J, Meyer H, Stolk E, Tan E, editors. Complexity Theories of Cities Have Come of Age: An Overview with Implications to Urban Planning and Design. *Springer*, Heidelberg 2012:7-20.

Hallemans A, Beccu S, Van Loock K, Ortibus E, Truijen S, Aerts P. Visual deprivation leads to gait adaptations that are age- and context-specific: I. Step-time parameters. *Gait Posture*. 2009;**30**(1):55-59.

Hanakawa T, Fukuyama H, Katsumi Y, Honda M, Shibasaki H. Enhanced lateral premotor activity during paradoxical gait in Parkinson's disease. *Ann Neurol*. 1999;**45**(3):329-36.

Hashimoto T. Speculation on the responsible sites and pathophysiology of freezing of gait. *Parkinsonism Relat Disord*. 2006;**12**:55-62.

Hausdorff JM, Peng CK, Ladin Z, Wei JY, Goldberger AL. Is walking a random walk? Evidence for long-range correlations in stride interval of human gait. *J Appl Physiol*. 1995;**78**(1):349-58.

Hausdorff JM, Purdon PL, Peng CK, Ladin Z, Wei JY, Goldberger AL. Fractal dynamics of human gait: stability of long-range correlations in stride interval fluctuations. *J Appl Physiol*. 1996;**80**(5):1448-57.

Hausdorff JM, Mitchell SL, Firtion R, Peng CK, Cudkowicz ME, Wei JY, Goldberger AL. Altered fractal dynamics of gait: reduced stride-interval correlations with aging and Huntington's disease. *J Appl Physiol*. 1997;**82**(1):262-69.

Hausdorff JM. Gait variability: methods, modeling and meaning. *J Neuroeng Rehabil*. 2005;**2**(1):1-9.

Häusser M, Clark BA. Tonic synaptic inhibition modulates neuronal output pattern and spatiotemporal synaptic integration. *Neuron*. 1997;**19**(3):665-78.

Herman T, Giladi N, Gurevich T, Hausdorff JM. Gait instability and fractal dynamics of older adults with a "cautious" gait: why do certain older adults walk fearfully? *Gait Posture*. 2005;**21**(2):178-85.

Hof A, Gazendam M, Sinke W. The condition for dynamic stability. *J Biomech*. 2005;**38**(1):1-8.

Hollands M, Marple-Horvat D. Visually guided stepping under conditions of step cycle-related denial of visual information. *Exp Brain Res*. 1996;**109**(2):343-56.

Holmberg J, Karlberg M, Fransson PA, Magnusson M. Phobic postural vertigo: body sway during vibratory proprioceptive stimulation. *Neuroreport*. 2003;**14**(7):1007-11.

Holmberg J, Karlberg M, Harlacher U, Magnusson M. Experience of handicap and anxiety in phobic postural vertigo. *Acta Otolaryngol*. 2005;**125**(3):270-75.

Holt KG, Hamill J, Andres RO. The force-driven harmonic oscillator as a model for human locomotion. *Hum Mov Sci*. 1990;**9**(1):55-68.

Holt KG, Jeng SF, Ratcliffe R, Hamill J. Energetic cost and stability during human walking at the preferred stride frequency. *J Mot Behav*. 1995;**27**(2):164-78.

Horak FB, Nashner LM. Central programming of postural movements: adaptation to altered support-surface configurations. *J Neurophysiol*. 1986;**55**(6):1369-81.

Horak FB, Nashner L, Diener H. Postural strategies associated with somatosensory and vestibular loss. *Exp Brain Res*. 1990;**82**(1):167-77.

Horak FB, Diener H. Cerebellar control of postural scaling and central set in stance. *J Neurophysiol*. 1994a;**72**(2):479-93.

Horak FB, Shupert C, Dietz V, Horstmann G. Vestibular and somatosensory contributions to responses to head and body displacements in stance. *Exp Brain Res*. 1994b;**100**(1):93-106.

Horak FB, Macpherson JM. Postural orientation and equilibrium. In: Smith JL, ed. Handbook of Physiology: Section 12 – Exercise: Regulation and Integration of Multiple Systems. New York, NY: *Oxford University Press*. 1996:255-92.

Horak FB, Henry SM, Shumway-Cook A. Postural perturbations: new insights for treatment of balance disorders. *Phys Ther*. 1997;**77**(5):517-33.

Horak FB, Dimitrova D, Nutt JG. Direction-specific postural instability in subjects with Parkinson's disease. *Exp Neurol*. 2005;**193**(2):504-21.

Hoyt DF, Taylor CR. Gait and the energetics of locomotion in horses. *Nature*. 1981;**292**:239-40.

Huppert D, Grill E, Brandt T. Down on heights? One in three has visual height intolerance. *J Neurol*. 2013;**260**(2):597-604.

Huxham FE, Goldie PA, Patla AE. Theoretical considerations in balance assessment. *Aust J Physiother*. 2001;**47**(2):89-101.

Ilg W, Golla H, Thier P, Giese MA. Specific influences of cerebellar dysfunctions on gait. *Brain*. 2007;**130**(3):786-98.

Ilg W, Giese M, Gizewski E, Schoch B, Timmann D. The influence of focal cerebellar lesions on the control and adaptation of gait. *Brain*. 2008;**131**(11):2913-27.

Ilg W, Timmann D. Gait ataxia – specific cerebellar influences and their rehabilitation. *Mov Disord*. 2013;**28**(11):1566-75.

Inglis JT, Horak FB, Shupert CL, Jones-Rycewicz C. The importance of somatosensory information in triggering and scaling automatic postural responses in humans. *Exp Brain Res*. 1994;**101**(1):159-64.

Inglis JT, Shupert CL, Hlavacka F, Horak FB. Effect of galvanic vestibular stimulation on human postural responses during support surface translations. *J Neurophysiol*. 1995;**73**(2):896-901.

Ishikawa K, Edo M, Terada N, Okamoto Y, Togawa K. Gait analysis in patients with vertigo. *Eur Arch Otorhinolaryngol*. 1993; **250**(4):229-32.

Ito M. The cerebellum and neural control. *Raven Press*, New York; 1984.

Ives AR. Measuring resilience in stochastic systems. *Ecol Monogr*. 1995;**65**(2):217-33.

Jacobs J, Horak FB. Cortical control of postural responses. *J Neural Transm*. 2007;**114**(10):1339-48.

Jahn K, Strupp M, Schneider E, Dieterich M, Brandt T. Differential effects of vestibular stimulation on walking and running. *Neuroreport*. 2000;**11**(8):1745-48.

Jahn K, Strupp M, Schneider E, Dieterich M, Brandt T. Visually induced gait deviations during different locomotion speeds. *Exp Brain Res*. 2001;**141**(3):370-74.

Jahn K, Deutschländer A, Stephan T, Strupp M, Wiesmann M, Brandt T. Brain activation patterns during imagined stance and locomotion in functional magnetic resonance imaging. *Neuroimage*. 2004;**22**(4):1722-31.

Jahn K, Deutschländer A, Stephan T, Kalla R, Hüfner K, Wagner J, Strupp M, Brandt T. Supraspinal locomotor control in quadrupeds and humans. *Prog Brain Res*. 2008a;**171**:353-62.

Jahn K, Deutschlander A, Stephan T, Kalla R, Wiesmann M, Strupp M, Brandt T. Imaging human supraspinal locomotor centers in brainstem and cerebellum. *Neuroimage*. 2008b;**39**(2):786-92.

James EG. A model of postural coordination dynamics. *Gait Posture*. 2014;**39**(1):194-97.

Jeka JJ, Oie KS, Kiemel T. Multisensory information for human postural control: integrating touch and vision. *Exp Brain Res*. 2000;**134**(1):107-25.

Johansson R, Magnusson M, Akesson M. Identification of human postural dynamics. *IEEE Trans Biomed Eng*. 1988;**35**(10):858-69.

Jordan K, Challis JH, Newell KM. Walking speed influences on gait cycle variability. *Gait Posture*. 2007;**26**(1):128-34.

Kalla R, Glasauer S, Büttner U, Brandt T, Strupp M. 4-aminopyridine restores vertical and horizontal neural integrator function in downbeat nystagmus. *Brain*. 2007;**130**(9):2441-51.

Kantelhardt JW, Koscielny-Bunde E, Rego HH, Havlin S, Bunde A. Detecting long-range correlations with detrended fluctuation analysis. *Physica A*. 2001;**295**(3):441-54.

Kelso J, Scholz J, Schöner G. Nonequilibrium phase transitions in coordinated biological motion: critical fluctuations. *Phys Lett A*. 1986;**118**(6):279-84.

Kelso J. Dynamic Patterns: The Self Organization of Brain and Behaviour. *MIT Press*, Cambridge, MA. 1995.

Kempen GI, Todd CJ, Van Haastregt JC, Rixt Zijlstra G, Beyer N, Freiberger E, Hauer KA, Piot-Ziegler C, Yardley L. Cross-cultural validation of the Falls Efficacy Scale International (FES-I) in older people: results from Germany, the Netherlands and the UK were satisfactory. *Disabil Rehabil*. 2007;**29**(2):155-62.

Keshner MS. 1/f noise. *Proc IEEE*. 1982;**70**(3):212-18.

Kiss IZ, Zhai Y, Hudson JL, Zhou C, Kurths J. Noise enhanced phase synchronization and coherence resonance in sets of chaotic oscillators with weak global coupling. *Chaos*. 2003;**13**(1):267-78.

Koskimies K, Sutinen P, Aalto H, Starck J, Toppila E, Hirvonen T, Kaksonen R, Ishizaki H, Alaranta H, Pyykko I. Postural stability, neck proprioception and tension neck. *Acta Otolaryngol Suppl*. 1997;**529**:95-97.

Krafczyk S, Schlamp V, Dieterich M, Haberhauer P, Brandt T. Increased body sway at 3.5-8 Hz in patients with phobic postural vertigo. *Neurosci Lett*. 1999;**259**(3):149-52.

Krasovsky T, Banina MC, Hacmon R, Feldman AG, Lamontagne A, Levin MF. Stability of gait and interlimb coordination in older adults. *J Neurophysio*l. 2012;**107**(9):2560-69.

Krasovsky T, Lamontagne A, Feldman AG, Levin MF. Reduced gait stability in high-functioning poststroke individuals. *J Neurophysiol*. 2013;**109**(1):77-88.

Krebs DE, Goldvasser D, Lockert JD, Portney LG, Gill-Body KM. Is base of support greater in unsteady gait? *Phys Ther*. 2002;**82**(2):138-47.

Kugler G, Huppert D, Schneider E, Brandt T. How acrophobia impairs visual exploration and gait. *Nervenarzt*. 2013;**84**(10):1233-37.

Kugler PN, Turvey MT. Information, Natural Law and the Self-Assembly of Rhythmic Movement. *Erlbaum*, Hillsdale, NJ; 1987.

Kuo AD, Speers RA, Peterka RJ, Horak FB. Effect of altered sensory conditions on multivariate descriptors of human postural sway. *Exp Brain Res*. 1998;**122**(2):185-95.

Lackner JR, DiZio PA. Aspects of body self-calibration. *Trends Cogn Sci*. 2000;**4**(7):279-88.

Lake DE, Richman JS, Griffin MP, Moorman JR. Sample entropy analysis of neonatal heart rate variability. *Am J Physiol Regul Integr Comp Physiol*. 2002;**283**(3):R789-97.

Latash ML, Scholz JP, Schöner G. Toward a New Theory of Motor Synergies. *Motor Control*. 2007;**11**:276-308.

Laughton CA, Slavin M, Katdare K, Nolan L, Bean JF, Kerrigan DC, Phillips E, Lipsitz LA, Collins JJ. Aging, muscle activity, and balance control: physiologic changes associated with balance impairment. *Gait Posture*. 2003;**18**(2):101-08.

Lauk M, Chow CC, Pavlik AE, Collins JJ. Human balance out of equilibrium: nonequilibrium statistical mechanics in posture control. *Phys Rev Lett*. 1998;**80**(2):413-16.

Lee D, Lishman J. Visual proprioceptive control of stance. *J Hum Mov Stud*. 1975;**1**:87-95.

Lewko J. Assessment of muscle electrical activity in spinal cord injury subjects during quiet standing. *Spinal Cord*. 1996;**34**(3):158-63.

Li X, Aruin AS. The effect of short-term changes in the body mass on anticipatory postural adjustments. *Exp Brain Res*. 2007;**181**(2):333-46.

Lipsitz LA. Dynamics of stability the physiologic basis of functional health and frailty. *J Gerontol A Biol Sci Med Sci*. 2002;**57**(3):B115-25.

Löhle M, Schrempf W, Wolz M, Reichmann H, Storch A. Potassium channel blocker 4-aminopyridine is effective in interictal cerebellar symptoms in episodic ataxia type 2 – A video case report. *Mov Disord*. 2008;**23**(9):1314-16.

Lord SR. Visual risk factors for falls in older people. *Age Ageing*. 2006;**35**(Suppl 2):ii42-45.

Lugade V, Lin V, Chou LS. Center of mass and base of support interaction during gait. *Gait Posture*. 2011;**33**(3):406-11.

Macpherson JM, Inglis JT. Stance and balance following bilateral labyrinthectomy. *Prog Brain Res*. 1993;**97**:219-28.

Magnus R. Some results of studies in the physiology of posture. *Lancet*. 1926:531-36

Magnusson M, Enbom H, Johansson R, Wiklund J. Significance of pressor input from the human feet in lateral postural control: the effect of hypothermia on galvanically induced body-sway. *Acta Otolaryngol*. 1990;**110**(3-4):321-27.

Maki BE, Holliday PJ, Fernie GR. A posture control model and balance test for the prediction of relative postural stability. *IEEE Trans Biomed Eng*. 1987;**34**(10):797-810.

Maki BE, McIlroy WE. Influence of arousal and attention on the control of postural sway. *J Vestib Res*. 1996;**6**(1):53-59.

Maki BE. Gait changes in older adults: predictors of falls or indicators of fear. *J Am Geriatr Soc*. 1997;**45**(3):313-20.

Marco I, Augusto F, Giovanni M, Stefano P. Effects of visual deprivation on gait dynamic stability. *Scientific World Journal*. 2012:974560

Massion J. Movement, posture and equilibrium: interaction and coordination. *Prog Neurobiol*. 1992;**38**(1):35-56.

Mcgeer T. Passive Dynamic Walking. International Journal of Robotics Research. 1990;**9**(2):62-82.

Morasso PG, Baratto L, Capra R, Spada G. Internal models in the control of posture. *Neural Netw*. 1999;**12**(7):1173-80.

Mori S, Sakamoto T, Ohta Y, Takakusaki K, Matsuyama K. Site-specific postural and locomotor changes evoked in awake, freely moving intact cats by stimulating the brainstem. *Brain Res*. 1989;**505**(1):66-74.

Mori S, Matsui T, Kuze B, Asanome M, Nakajima K, Matsuyama K. Stimulation of a restricted region in the midline cerebellar white matter evokes coordinated quadrupedal locomotion in the decerebrate cat. *J Neurophysiol*. 1999;**82**(1):290-300.

Mori S, Matsuyama K, Mori F, Nakajima K. Supraspinal sites that induce locomotion in the vertebrate central nervous system. *Adv Neurol*. 2001;**87**:25-40.

Morton SM, Bastian AJ. Cerebellar control of balance and locomotion. *Neuroscientist*. 2004;**10**(3):247-59.

Mueller MJ, Minor SD, Sahrmann SA, Schaaf JA, Strube MJ. Differences in the gait characteristics of patients with diabetes and peripheral neuropathy compared with age-matched controls. *Phys Ther*. 1994;**74**(4):299-308.

Nashner LM. Balance adjustments of humans perturbed while walking. *J Neurophysiol*. 1980;**44**(4):650-64.

Nashner LM. Adaptation of human movement to altered environments. *Trends Neurosci*. 1982a;**5**:358-61.

Nashner LM, Black FO, Wall C. Adaptation to altered support and visual conditions during stance: patients with vestibular deficits. *J Neurosci*. 1982b;**2**(5):536-44.

Nashner LM, Forssberg H. Phase-dependent organization of postural adjustments associated with arm movements while walking. *J Neurophysiol*. 1986;**55**(6):1382-94.

Nashner LM. Practical biomechanics and physiology of balance. In: Jacobson GP, Newman CU, Kartush JM, editors. Handbook of Balance Function Testing. *Mosby-Year Book*, St Louis. 1993:261-79.

Newell KM, van Emmerik RE, Lee D, Sprague RL. On postural stability and variability. *Gait Posture*. 1993;**1**(4):225-30.

O'Connor SM, Kuo AD. Direction-dependent control of balance during walking and standing. *J Neurophysiol*. 2009;**102**(3):1411-19.

Oie KS, Kiemel T, Jeka JJ. Human multisensory fusion of vision and touch: detecting non-linearity with small changes in the sensory environment. *Neurosci Lett*. 2001;**315**(3):113-16.

Oie KS, Kiemel T, Jeka JJ. Multisensory fusion: simultaneous re-weighting of vision and touch for the control of human posture. *Brain Res Cogn Brain Res*. 2002;**14**(1):164-76.

Ouchi Y, Okada H, Yoshikawa E, Nobezawa S, Futatsubashi M. Brain activation during maintenance of standing postures in humans. *Brain*. 1999;**122**(2):329-38.

Owings TM, Grabiner MD. Step width variability, but not step length variability or step time variability, discriminates gait of healthy young and older adults during treadmill locomotion. *J Biomech*. 2004;**37**(6):935-38.

Pai YC, Patton J. Center of mass velocity-position predictions for balance control. *J Biomech*. 1997;**30**(4):347-54.

Pasman E, Murnaghan C, Bloem B, Carpenter M. Balance problems with Parkinson's disease: are they anxiety-dependent? *Neuroscience*. 2011;**177**:283-91.

Patla AE, Goodale MA. Obstacle avoidance during locomotion is unaffected in a patient with visual form agnosia. *Neuroreport*. 1996;**8**(1):165-68.

Patla AE. Understanding the roles of vision in the control of human locomotion. *Gait Posture*. 1997;**5**(1):54-69.

Paulus W, Straube A, Brandt T. Visual stabilization of posture physiological stimulus characteristics and clinical aspects. *Brain*. 1984;**107**(4):1143-63.

Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *Chaos*. 1995;**5**(1):82-87.

Peterka RJ. Postural control model interpretation of stabilogram diffusion analysis. *Biol Cybern*. 2000;**82**(4):335-43.

Peterka RJ. Sensorimotor integration in human postural control. *J Neurophysiol*. 2002;**88**(3):1097-118.

Pomper JK, Gebert L, Fischer M, Bunjes F, Thier P. Does chronic idiopathic dizziness reflect an impairment of sensory predictions of self-motion? *Frontiers in neurology*. 2013;**4**:181.

Pozzo T, Berthoz A, Lefort L. Head stabilization during various locomotor tasks in humans. *Exp Brain Res*. 1990;**82**(1):97-106.

Pozzo T, Levik Y, Berthoz A. Head and trunk movements in the frontal plane during complex dynamic equilibrium tasks in humans. *Exp Brain Res*. 1995;**106**(2):327-38.

Querner V, Krafczyk S, Dieterich M, Brandt T. Patients with somatoform phobic postural vertigo: the more difficult the balance task, the better the balance performance. *Neurosci Lett*. 2000;**285**(1):21-24.

Redfern MS, Schumann T. A model of foot placement during gait. *J Biomech*. 1994;**27**(11):1339-46.

Reed-Troy KL, Grabiner MD. Neuromuscular and Biomechanical Elements of Postural Equilibrium. In: Hausdorff JM and Alexander NB, editors. Gait Disorders Evaluation and Management. T*aylor and Francis Group*, Boca Raton:101-15.

Rhea CK, Rietdyk S. Visual exteroceptive information provided during obstacle crossing did not modify the lower limb trajectory. *Neurosci Lett*. 2007;**418**(1):60-65.

Richardson JK, Ching C, Hurvitz EA. The relationship between electromyographically documented peripheral neuropathy and falls. *J Am Geriatr Soc*. 1992;**40**(10):1008-12.

Richardson MJ, Schmidt R, Kay BA. Distinguishing the noise and attractor strength of coordinated limb movements using recurrence analysis. *Biol Cybern*. 2007;**96**(1):59-78.

Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol*. 2000;**278**(6):H2039-49.

Romberg MH. A Manual of the Nervous Diseases of Man. Sievering EH, trans. *Sydenham Society,* London. 1853.

Rossignol S, Dubuc R, Gossard J-P. Dynamic sensorimotor interactions in locomotion. *Physiol Rev*. 2006;**86**(1):89-154.

Salassa JR, Zapala DA. Love and fear of heights: the pathophysiology and psychology of height imbalance. *Wilderness Environ Med*. 2009;**20**(4):378-82.

Schaeffler F, Mueller M, Huppert D, Brandt T, Tiffe T, Grill E. Consequences of visual height intolerance for quality of life: a qualitative study. *Qual Life Res*. 2013:1-9.

Scheffer M, Bascompte J, Brock WA, Brovkin V, Carpenter SR, Dakos V, Held H, Van Nes EH, Rietkerk M, Sugihara G. Early-warning signals for critical transitions. *Nature*. 2009;**461**(7260):53-59.

Schniepp R, Wuehr M, Ackl N, Danek A, Brandt T, Strupp M, Jahn K. 4-Aminopyridine improves gait variability in cerebellar ataxia due to CACNA 1A mutation. *J Neurol*. 2011;**258**(9):1708-11.

Schniepp R, Wuehr M, Neuhaeusser M, Benecke AK, Adrion C, Brandt T, Strupp M, Jahn K. 4-Aminopyridine and cerebellar gait: a retrospective case series. *J Neurol*. 2012a;**259**(11):2491-93.

Schniepp R, Wuehr M, Neuhaeusser M, Kamenova M, Dimitriadis K, Klopstock T, Strupp M, Brandt T, Jahn K. Locomotion speed determines gait variability in cerebellar ataxia and vestibular failure. *Mov Disord*. 2012b;**27**(1):125-31.

Schniepp R, Wuehr M, Pradhan C, Novozhilov S, Krafczyk S, Brandt T, Jahn K. Nonlinear variability of body sway in patients with phobic postural vertigo. *Frontiers in neurology*. 2013;**4**:115.

Schniepp R, Wuehr M, Huth S, Pradhan C, Brandt T, Jahn K. Gait characteristics of patients with phobic postural vertigo: effects of fear of falling, attention, and visual input. *J Neurol*. 2014a; **261**(4):738-46.

Schniepp R, Wuehr M, Schlick C, Huth S, Pradhan C, Dieterich M, Brandt T, Jahn K. Increased gait variability is associated with the history of falls in patients with cerebellar ataxia. *J Neurol*. 2014b;**261**(1):213-23.

Schöner G, Kelso J. Dynamic pattern generation in behavioral and neural systems. *Science*. 1988;**239**(4847):1513-20.

Schöner G, Jiang WY, Kelso J. A synergetic theory of quadrupedal gaits and gait transitions. *J Theor Biol*. 1990;**142**(3):359-91.

Scott D, Dzendolet E. Quantification of sway in standing humans. *Agressologie*. 1972;**13**:35-40.

Sherrington CS. Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. *J Physiol*. 1910; **40**(1-2):28-121.

Shik ML, Severin F, Orlovsky GN. Control of walking and running by means of electric stimulation of the midbrain. *Biofizika*. 1965;**11**(4):659-66.

Shik ML, Orlovsky GN. Neurophysiology of locomotor automatism. *Physiol Rev*. 1976;**56**(3):465-501.

Shumway-Cook A, Woollacott MH. Motor Control: Translating Research Into Clinical Practice. *Wolters Kluwer Health/ Lippincott Williams & Wilkins*, Baltimore, MD. 2012.

Sinkjær T, Andersen JB, Larsen B. Soleus stretch reflex modulation during gait in humans. *J Neurophysiol*. 1996;**76**(2):1112-20.

Slifkin AB, Newell KM. Noise, information transmission, and force variability. *J Exp Psychol Hum Percept Perform*. 1999;**25**(3):837-51.

Smith AM. The coactivation of antagonist muscles. *Can J Physiol Pharmacol*. 1981;**59**(7):733-47.

Smith LB, Thelen E. A dynamic systems approach to development: Applications. *MIT Press*, Cambridge, MA.1993.

Staab JP, Ruckenstein MJ. Expanding the differential diagnosis of chronic dizziness. *Arch Otolaryngol Head Neck Surg*. 2007; **133**(2):170-76.

Stapley PJ, Drew T. The pontomedullary reticular formation contributes to the compensatory postural responses observed following removal of the support surface in the standing cat. *J Neurophysiol*. 2009;**101**(3):1334-50.

Strogatz S. Nonlinear dynamics and chaos: with applications to physics, biology, chemistry and engineering. *Perseus Books*, Cambridge, MA. 2001.

Strupp M, Kalla R, Dichgans M, Freilinger T, Glasauer S, Brandt T. Treatment of episodic ataxia type 2 with the potassium channel blocker 4-aminopyridine. *Neurology*. 2004;**62**(9):1623-25.

Takakusaki K, Habaguchi T, Ohtinata-Sugimoto J, Saitoh K, Sakamoto T. Basal ganglia efferents to the brainstem centers controlling postural muscle tone and locomotion: a new concept for understanding motor disorders in basal ganglia dysfunction. *Neuroscience*. 2003;**119**(1):293-308.

Takakusaki K, Saitoh K, Harada H, Kashiwayanagi M. Role of basal ganglia – brainstem pathways in the control of motor behaviors. *Neurosci Res*. 2004;**50**(2):137-51.

Takakusaki K, Tomita N, Yano M. Substrates for normal gait and pathophysiology of gait disturbances with respect to the basal ganglia dysfunction. *J Neurol*. 2008;**255**(4):19-29.

Takakusaki K, Obara K, Nozu T, Okumura T. Modulatory effects of the GABAergic basal ganglia neurons on the PPN and the muscle tone inhibitory system in cats. *Arch Ital Biol*. 2011;**149**(4):383-405.

Takakusaki K. Neurophysiology of gait: From the spinal cord to the frontal lobe. *Mov Disord*. 2013;**28**(11):1483-91.

Terrier P, Turner V, Schutz Y. GPS analysis of human locomotion: further evidence for long-range correlations in stride-to-stride fluctuations of gait parameters. *Hum Mov Sci*. 2005;**24**(1):97-115.

Thach TW, Bastian AJ. Role of the cerebellum in the control and adaptation of gait in health and disease. *Prog Brain Res*. 2004;**143**:353-66.

Thelen E, Smith LB, Karmiloff-Smith A, Johnson MH. A dynamic systems approach to the development of cognition and action. *MIT Press*, Cambridge, MA.1994.

Timmann D, Horak FB. Prediction and set-dependent scaling of early postural responses in cerebellar patients. *Brain*. 1997; **120**(2):327-37.

Ting LH, McKay JL. Neuromechanics of muscle synergies for posture and movement. *Curr Opin Neurobiol*. 2007;**17**(6):622-28.

Tjernstrom F, Fransson PA, Holmberg J, Karlberg M, Magnusson M. Decreased postural adaptation in patients with phobic postural vertigo – an effect of an "anxious" control of posture? Neurosci Lett. 2009;**454**(3):198-202.

Townsend MA. Biped gait stabilization via foot placement. *J Biomech*. 1985;**18**(1):21-38.

Turvey MT. Coordination. *Am Psychol*. 1990;**45**(8):938-53.

Wagenaar RC, van Emmerik RE. Dynamics of pathological gait. *Hum Mov Sci*. 1994;**13**(3):441-71.

Walter JT, Alviña K, Womack MD, Chevez C, Khodakhah K. Decreases in the precision of Purkinje cell pacemaking cause cerebellar dysfunction and ataxia. *Nat Neurosci*. 2006;**9**(3):389-97.

West BJ, Scafetta N. Nonlinear dynamical model of human gait. *Physical Review E*. 2003;**67**(5):051917.

Whitney S, Hudak M, Marchetti G. The dynamic gait index relates to self-reported fall history in individuals with vestibular dysfunction. *J Vestib Res*. 2000;**10**(2):99-105.

Wiesendanger M, Hummelsheim H, Bianchetti M, Chen D, Hyland B, Maier V, Wiesendanger R. Input and output organization of the supplementary motor area. *CIBA Found Symp*. 1987;**132**:40-62.

Winter DA. Biomechanical motor patterns in normal walking. *J Mot Behav*. 1983;**15**(4):302-30.

Winter DA, Patla AE, Frank JS, Walt SE. Biomechanical walking pattern changes in the fit and healthy elderly. *Phys Ther*. 1990;**70**(6):340-47.

Winter DA. Human balance and posture control during standing and walking. *Gait Posture*. 1995a;**3**(4):193-214.

Winter DA. A. B. C. (Anatomy, Biomechanics and Control) of Balance During Standing and Walking. *Waterloo Biomechanics*, Waterloo. 1995b.

Womack MD, Khodakhah K. Active contribution of dendrites to the tonic and trimodal patterns of activity in cerebellar Purkinje neurons. *J Neurosci*. 2002;**22**(24):10603-12.

Woollacott MH, Tang PF. Balance control during walking in the older adult: research and its implications. *Phys Ther*. 1997; **77**(6):646-60.

Wuehr M, Pradhan C, Novozhilov S, Krafczyk S, Brandt T, Jahn K, Schniepp R. Inadequate interaction between open- and closed-loop postural control in phobic postural vertigo. *J Neurol*. 2013a;**260**(5):1314-23.

Wuehr M, Schniepp R, Ilmberger J, Brandt T, Jahn K. Speed-dependent temporospatial gait variability and long-range correlations in cerebellar ataxia. *Gait Posture*. 2013b;**37**(2):214-18.

Wuehr M, Schniepp R, Pradhan C, Ilmberger J, Strupp M, Brandt T, Jahn K. Differential effects of absent visual feedback control on gait variability during different locomotion speeds. *Exp Brain Res*. 2013c;**224**(2):287-94.

Wuehr M, Kugler G, Schniepp R, Eckl M, Pradhan C, Jahn K, Huppert D, Brandt T. Balance control and anti-gravity muscle activity during the experience of fear at heights. *Physiol Rep*. 2014a;**2**(2).

Wuehr M, Pradhan C, Brandt T, Jahn K, Schniepp R. Patterns of optimization in single- and inter-leg gait dynamics. *Gait Posture*. 2014b;**39**(2):733-38.

Wuehr M, Schniepp R, Schlick C, Huth S, Pradhan C, Dieterich M, Brandt T, Jahn K. Sensory loss and walking speed related factors for gait alterations in patients with peripheral neuropathy. *Gait Posture*. 2014c;**39**(3):852-58.

Xerri C, Borel L, Barthelemy J, Lacour M. Synergistic interactions and functional working range of the visual and vestibular systems in postural control: neuronal correlates. *Prog Brain Res*. 1988;**76**:193-203.

Yamasaki M, Sasaki T, Tsuzuki S, Torii M. Stereotyped pattern of lower limb movement during level and grade walking on treadmill. *Ann Physiol Anthropol*. 1984;**3**(4):291-6.

Yamasaki M, Sasaki T, Torii M. Sex difference in the pattern of lower limb movement during treadmill walking. *Eur J Appl Physiol*. 1991;**62**(2):99-103.

Zarrugh MY, Todd FN, Ralston HJ. Optimization of energy expenditure during level walking. *Eur J Appl Physiol Occup Physiol*. 1974;**33**(4):293-306.

Zehr EP, Stein RB. What functions do reflexes serve during human locomotion? *Prog Neurobiol*. 1999;**58**(2):185-205.

Zhou C, Kurths J, Kiss IZ, Hudson JL. Noise-enhanced phase synchronization of chaotic oscillators. *Phys Rev Lett*. 2002;**89**(1):14101.

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Curriculum Vitae

Personal data	Max Wühr, born at the 2. January 1986, Munich

Education

Sept. 1992 to July 1996	Primary school *Grundschule an der Blutenburgstraße*
Sept. 1996 to June 2005	Secondary school *Luisengymnasium* Abitur (grade: 1.1) in June 2005
Since October 2005	Studies in physics, *Ludwig-Maximilians-Universität*
Since October 2005	Studies in philosophy, *Ludwig-Maximilians-Universität*
August 2008	Bachelor in physics (grade: 1.1) Bachelor Thesis: "Light Driven Microfluidic Flow in Ice" (grade: 1.0)
Since October 2008	Elite graduate program *Neurosciences, Ludwig-Maximilians-Universität*
September 2010	Master in Neurosciences (grade: 1.3) Master Thesis: "Multisensory Regulation of Gait Variability" (grade: 1.0)
July 2011	Magister in philosophy (grade 1.1) Magister Thesis: "Wahrnehmungsintentionalität und Handlungsfreiheit" (grade: 1.2)

Internship

March 2007	Internship at the hospital *Barmherzige Brüder*, Munich

Employment

since September 2009	Research assistant at the *Klinikum Großhadern,* Munich in the work group of Prof. Dr. med. Dr. h. c. Thomas Brandt and Prof. Dr. med. Klaus Jahn

Scholarships

since June 2005	*e-fellows.net* scholarship (www.e-fellows.net)
June 2005	Studiengenossenverband Luisengymnasium scholarship "For social commitment and outstanding achievements at school"
	Award of the German Physical Society
January 2009 to Sept. 2011	Studienstiftung des Deutschen Volkes
March 2009 to Sept. 2010	Max-Weber-Programm Bayern

Publications

Schniepp R, **Wuehr M**, Huth S, Pradhan C, Brandt T, Jahn K. Gait characteristics of patients with phobic postural vertigo: effects of fear of falling, attention, and visual input. *J Neurol.* 2014; **261**(4):738-46.

Wuehr M, Kugler G, Schniepp R, Eckl M, Jahn K, Huppert D, Brandt T. Balance control and anti-gravity muscle activity during the experience of fear at heights. *Physiol Rep*. 2014;**2**(2).

Wuehr M, Schniepp R, Schlick C, Huth S, Dieterich M. Brandt T, Jahn K. Sensory loss and walking speed related factors for gait alterations in patients with peripheral neuropathy. *Gait Posture*. 2014;**39**(3):852-58.

Schniepp R, **Wuehr M**, Schlick C, Huth S, Dieterich M. Brandt T, Jahn K. Increased gait variability is associated with a higher risk of falls in patients with cerebellar ataxia. *J Neurol*. 2014;**261**(1):213-23.

Wuehr M, Pradhan C, Brandt T, Jahn K, Schniepp R. Patterns of optimization in single- and inter-leg gait dynamics. *Gait Posture*. 2014;**39**(2):733-38.

Pradhan C, **Wuehr M**, Neuhaeusser M, Huth S, Brandt T, Jahn K, Schniepp R. Multivariate gait data analysis: Comparison between healthy adults of different age groups. *J Neurosci Neuroeng*. 2013;**2**(6):542-49.

Schniepp R*, **Wuehr M***, Pradhan C, Novozhilov S, Krafczyk S, Brandt T, Jahn K. Nonlinear variability of body sway in patients with Phobic Postural Vertigo. *Frontiers in neurology*. 2013;**4**:115.

*equal contribution

Wuehr M, Pradhan C, Novozhilov S, Krafczyk S, Brandt T, Jahn K, Schniepp R. Inadequate interaction between open- and closed-loop postural control in phobic postural vertigo. *J Neurol*. 2013;**260**(5):1314-23.

Wuehr M, Schniepp R, Ilmberger J, Strupp M, Brandt T, Jahn K. Differential effects of absent visual feedback control on gait variability during different locomotion speeds. *Exp Brain Res*. 2013;**224**(2):287-94.

Schniepp R, Jackl V, **Wuehr M**, Havla J, Kümpfel T, Dieterich M, Strupp M, Jahn K. Treatment with 4-Aminopyridine improves upper limb tremor of a patient with multiple sclerosis: a video case report. *Mult Scler*. 2013;**19**(4):506-8.

Wuehr M, Schniepp R, Ilmberger J, Brandt T, Jahn K. Speed-dependent temporospatial gait variability and long-range correlations in cerebellar ataxia. *Gait Posture*. 2013;**37**(2):214-18.

Schniepp R, **Wuehr M**, Neuhaeusser M, Benecke AK, Adrion C, Brandt T, Jahn K. 4-Aminopyridine and cerebellar gait: a retrospective case series. *J Neurol*. 2012;**259**(11):2491-93.

Schniepp R, **Wuehr M**, Neuhaeusser M, Kamenova M, Dimitriadis K, Klopstock T, Strupp M, Brandt T, Jahn K. Locomotion speed determines gait variability in cerebellar ataxia and vestibular failure. *Mov Disord*. 2012;**27**(1):125-31.

Schniepp R, **Wuehr M**, Ackl N, Danek A, Brandt T, Strupp M, Jahn K. 4-Aminopyridine improves gait variability in cerebellar ataxia due to CACNA 1A mutation. *J Neurol*. 2011;**258**(9):1708-11.

Weinert FM, **Wuehr M**, Braun D. Light driven microflow in ice. *Appl Phys Lett*. 2009;**94**(11):113901.*

*Picked by Nature Photonics 3, 242-243 2009.

Congress Presentations

Wuehr M, Kugler G, Schniepp R, Huppert D, Brandt T. Postural control changes in visual height intolerance: body sway and anti-gravity muscle activity. EFNS-ENS Congress, Istanbul 2014.

Wuehr M, Kugler G, Schniepp R, Huppert D, Brandt T. Physiologic alterations associated with visual height intolerance: balance control and muscle activity. DGKN Congress, Berlin 2014.

Wuehr M, Pradhan C, Schniepp R, Jahn K. Peripheral neuropathy alters gait variability in a speed-dependent manner. DGN Congress, Dresden 2013.

Wuehr M, Pradhan C, Jahn K, Schniepp R. Influences on gait variability in patients with polyneuropathy. ENS Congress, Barcelona 2013.

Wuehr M, Schniepp R, Brandt T, Jahn K. Gestörte Interaktion zwischen der Open- und Closed-Loop Haltungskontrolle bei phobischem Schwankschwindel. DGKN Congress, Leipzig 2013.

Wuehr M, Schniepp R, Pradhan C, Novozhilov S, Krafczyk S. Brandt T, Jahn K. Nonlinear variability of body sway in patients with Phobic Postural Vertigo. DGN Congress, Hamburg 2012.

Wuehr M, Schniepp R. Visual perturbation influences gait variability in healthy walkers. EFNS Congress, Stockholm 2012.

Wuehr M, Schniepp R. 4-Aminopyridine improves cerebellar tremor in a patient with multiple sclerosis. EFNS Congress, Stockholm 2012.

Wuehr M, Schniepp R, Ilmberger J, Brandt T, Jahn K. Effects of visual perturbation on gait depend on locomotion speed. Bárány Society Congress, Uppsala 2012.

Wuehr M, Schniepp R, Ilmberger J, Brandt T, Jahn K. Visual perturbation causes alterations in the gait variability during different locomotion speeds. ISPGR Congress, Trondheim 2012.

Wuehr M, Schniepp R, Ilmberger J, Brandt T, Jahn K. Effects of visual perturbation on the gait variability during different locomotion speeds. DGKN Congress, Köln 2012.

Wuehr M, Schniepp R. 4-Aminopyridine improves cerebellar tremor in a patient with multiple sclerosis. DGKN Congress, Köln 2012.

Wuehr M, Schniepp R., Ilmberger J, Jahn K. Langzeitkorrelationen im Gangmuster von Patienten mit zerebellärer Ataxie. DGKN Congress, Münster 2011.

Wuehr M, Neuhäußer M, Schniepp R, Jahn K. A new tool for data analysis for GAITRite. Gait & Mental Function Congress, Washington D.C. 2010.

Wuehr M, Neuhäußer M, Schniepp R, Jahn K. A new tool for data analysis for GAITRite. European GAITRite Meeting, Basel 2009.