

# **Sensitivity to Visuomotor Prediction Errors During Precision Walking**

by

**Rodrigo S Maeda**

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# Approval

**Name:** Rodrigo S Maeda  
**Degree:** Master of Science (BPK)  
**Title:** *Sensitivity to visuomotor prediction errors during precision walking*  
**Examining Committee:** Chair: Dr. Will Cupples  
Professor

**Dr. Dan Marigold**  
Senior Supervisor  
Associate Professor

---

**Dr. Max Donelan**  
Supervisor  
Associate Professor

---

**Dr. Shawn O' Connor**  
Supervisor  
Research Associate  
Department of Bioengineering  
University of California San Diego

---

**Dr. Tania Lam**  
External Examiner  
Associate Professor  
School of Kinesiology  
University of British Columbia

---

**Date Defended/Approved:** \_\_\_\_\_

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## **Abstract**

All human movements happen in the face of uncertainty. The objective of this thesis was to determine how the nervous system deals with sensorimotor uncertainty when adapting to visuomotor perturbations during walking. We asked subjects to walk and step on a target while wearing prism goggles that shifted the perception of the target's location. We manipulated uncertainty by varying the strength and perturbation direction of the prism lenses on a trial-by-trial basis in three conditions: no, low and high noise. We measured lateral end-point errors of foot placement from the target in a visuomotor adaptation paradigm with baseline, adaptation and post-adaptation phases. Results showed increases in error variability, slower adaptation rates, and smaller errors in the first adaptation trial when increasing uncertainty. These results suggest that the nervous system relies on a predictive mechanism, which is sensitive to errors, and weights prior experiences to adapt walking.

**Keywords:** Forward Models, Prediction Error Sensitivity, Prior, Uncertainty, Visuomotor Adaptation, Walking.

*I would like to dedicate this thesis to my mother, who  
comprehended my absence for the purpose of this  
project.*

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## List of Acronyms

CPGs	Central pattern generators
FEF	Frontal eye field
GTO	Golgi tendon organs
ML	Medial-lateral
MLR	Mesencephalic locomotor region
PET	Positron emission tomography
PPC	Posterior parietal cortex
RMSE	Root mean square error

# **Chapter 1. Literature Review**

## **1.1. Overview**

Visually guided limb movements require the brain to maintain a precise relationship between a perceived target location and the predicted motor command required to arrive at it. This internal representation or visuomotor mapping models the environmental, sensory, and motor systems and is crucial for performing smooth ballistic movements, which are not possible using sensory feedback alone (Shadmehr et al., 2010). Nevertheless, in many circumstances environmental and body systems can change, such as the result of new prescription glasses, eye disease, or muscle impairments, causing movement errors. Movement errors inform the nervous system that the outcome of its action did not match the expected or desired action, leading to a sensory prediction error that drives adaptation (Tseng et al., 2007; Shadmehr et al., 2010). Motor adaptation is a process of recalibrating the visuomotor mapping to restore the former or desired level of performance. A major limitation to this process is that the mechanisms underlying sensorimotor control and adaptation are considerably affected by uncertainty. Uncertainty in sensorimotor control emerges from unpredicted environmental events, and as a result of sensorimotor constraints, including delays and noise within sensory feedback and motor command signals (van Beers et al., 2002; Faisal et al., 2008).

Uncertainty increases movement variability but also affects how the nervous system might interpret and use movement error feedback. In particular, when a motor command is issued to achieve a goal and a movement error is observed, the real cause of this error is unknown, and could be the result of a miscalibration, random sensorimotor noise, or a combination of both. Miscalibration errors result from an incorrect, or biased, internal visuomotor mapping. Thus, reducing movement errors to zero in this case requires the nervous system to adapt the visuomotor relationship by

updating the visual estimate of the target and the motor commands required to achieve it. Conversely, random sensorimotor noise corrupts all sensory input and motor output signals in the nervous system, which in turn leads to an increase in movement error variability despite the fact that the average error is zero. In this case, if the nervous system attempts to compensate and reduce movement errors after each movement, movement variability would instead drastically increase, dragging movements away from the average estimated location on a trial-by-trial basis. Reducing errors in this case essentially requires ignoring recent movement errors and instead considering the history of previous movements. In cases where both miscalibration and random noise are present, their relative sizes determine whether the optimal strategy is to place relatively more or less importance on recent movement errors over the history of previous movements. Given that sensorimotor signals are inherently noisy, and that the amount of noise may change with age, disease, and size of the motor commands, any perturbation to the normal visuomotor mapping that requires recalibration happens in the face of random amounts of noise and variability. Thus, the nervous system is left with the problem of identifying the cause of ambiguous movement errors and the strategy to improve movement accuracy.

Experimentally, prism glasses are used to shift the visual perception of objects, and thus disrupt the normal visuomotor mapping. When attempting to move to the perceived location of a target in the environment, movement errors are observed, allowing the study of how the nervous system interprets and uses those errors to control and adapt subsequent movements. By shifting the visual perception continuously towards the same direction, or randomly shifting the visual perception to multiple directions with a constant mean, it is possible to manipulate the cause of those errors, and create a bias (miscalibration) or an increase in variance (random sensorimotor noise) in the visuomotor mapping, respectively. These conditions help identify what strategies the nervous system may undertake when adapting in the face of random sensorimotor noise and uncertainty. Indeed, research has shown that uncertainty determines visuomotor adaptation of reaching movements and leads to the development of several models of how the brain might incorporate experience from previous trials (Baddeley et al., 2003; Burge et al., 2008). Nevertheless, on a daily basis the nervous system is faced with the problem of controlling and adapting different types of

movements, with different groups of muscles, joints and end-effectors. Thus, to fully understand how the nervous system works it is fundamental to investigate how multiple classes of movements are controlled in different contexts.

Locomotion and reaching behaviours have long been treated as distinct motor tasks. Indeed, as opposed to many reaching actions, locomotion requires the tight coordination of two limbs under whole-body balancing constraints. Previous research has predominantly studied human locomotion from the perspective that its control is dominated by reflexive, pattern generating, and balancing circuits located in the spinal cord and brainstem (Rossignol, 2006). Conversely, studies in reaching have instead considered that the precise and ballistic nature of arm movements require higher-level cortical control. Despite these differences, it is hypothesized that reaching likely evolved from quadrupedal locomotion (Georgopoulos and Grillner, 1989; Dietz, 2002). Both require precise control of either the hand or foot to targets in the environment, and rely on integration of sensory feedback about the location of the effectors and the target to plan the movements. This suggests that the neural control of upper and lower limbs may share a common framework. In this thesis, we approached the control of walking from the perspective of the framework of internal models and state estimation; a framework developed using eye and hand reaching tasks (Shadmehr and Mussa-Ivaldi, 1994; Wolpert et al., 1995; Shadmehr et al., 2010). This framework suggests that sensory feedback is weighted by its reliability or uncertainty and combined with prior experiences to control and adapt movements. Thus, the objective of this thesis is to determine whether sensorimotor uncertainty dictates how the brain adapts during visually guided walking. We hypothesize that by increasing visuomotor mapping uncertainty an internal model for the control of walking becomes less sensitive to error feedback, adapting slower to a systematic change in the visuomotor mapping.

In the literature review for this thesis, the first section provides a comparative perspective between reaching and walking. This section recognizes the challenges that the nervous system faces when controlling these two types of movements, but focuses on how the neural control of upper and lower limbs may share a common framework for movement control. The second section provides an overview of the internal models (state estimation) framework, describing its function, subdivisions, and explanations for

movement control. The third section focuses on the paradigm of visuomotor adaptation within the framework of internal models. In particular, this section shows how this paradigm can be used to study the control of different classes of movements. The fourth and last section introduces the problem of uncertainty and the model techniques generally used to study the strategies the nervous system may undertake when controlling and adapting movements.

## **1.2. Locomotion and Reaching: A Comparative Perspective**

Over the course of evolution, humans evolved to use bipedal locomotion, and developed more specialized hand functions, such as reaching and grasping. These abilities, which require higher demands of precision in the control of each limb, are thought to happen together with an increase in cortical involvement in movement control (Dietz, 2002; Dietz and Michel, 2009). Nevertheless, it has been hypothesized that the basic control mechanisms have remained in humans. Research has shown similar spinal mechanisms between cats and humans in upper and lower limbs (Duysens and Van de Crommert, 1998). In addition, multiple brain regions were also demonstrated to play similar roles in the control of both foot and arm movements (Leoné et al., 2014). This perspective brings forth the idea that similar spinal, cortical and subcortical neural networks may be shared during the control of arm and foot movements.

Reaching and walking are subject to distinct task constraints. To control walking, the nervous system is faced with considerable balance constraints and the need to coordinate muscles of the whole body while ensuring that the feet are placed in appropriate locations (Patla, 2003). This constraint happens because the nervous system must control the center of mass within the borders of a small and moving base of support (Nielsen, 2003; Patla, 2003). Furthermore, walking requires tight interlimb coordination, involving complex activations of agonists and antagonists muscles in a rhythmic movement pattern (Nielsen, 2003; Zehr and Duysens, 2004). The resultant is a movement that has to deal with these constraints in the face of the degrees of freedom of the joints involved, which dictate trajectories, velocity and acceleration of a particular movement (Wolpert and Ghahramani, 2000; Guigon et al., 2007). Reaching, conversely, requires demands of balance as the nervous system must control the muscles of the

trunk under a static base of support (Trivedi et al., 2010). In addition, reaching movements are discrete to targets in the environment, involving a reduced demand of interlimb coordination and distinct dynamics as compared to locomotion. These differences led investigations in locomotion and reaching to two distinct avenues of research. Human locomotion has been largely studied from the perspective that the control of the tight coupling between two effectors is dominated by reflexive, pattern generating, and balancing circuits located in the spinal cord and brainstem (Rossignol, 2006). On the other hand, studies in reaching have considered that precise and ballistic arm motions result from higher-level cortical control. Despite these differences, there are many key similarities over the steps of how these movements are planned. Both reaching and walking are goal directed movements. This requires vision to localize the targets that could be either a cup of coffee or a stepping-stone for reaching and walking, respectively. In addition, a weighting of vision and proprioception sensory information must localize the limb's state (Sober and Sabes, 2005; Marigold, 2008). This sensory feedback then needs to be converted into coordinates appropriate for movement, which entails computing a difference vector (distance vector) between the target and limb locations (Shadmehr and Wise, 2005). These similarities suggest that similar networks are in play in the control of upper and lower limbs (Georgopoulos and Grillner, 1989; Dietz, 2002).

Research in quadrupedal locomotion has long shown that the spinal cord plays a critical role in how movements are controlled during locomotion. In particular, neural networks within the spinal cord known as Central pattern generators (CPGs) have been identified as a main structure for generating locomotor like patterns even in the absence of afferent feedback signals (Duysens and Van de Crommert, 1998; Rossignol, 2006). When afferent feedback signals were removed either through injection of drugs or nerve transection, this spinal network generated the rhythmic patterns of agonist and antagonist muscle activities similar to intact animals during locomotion (Duysens and Van de Crommert, 1998; Rossignol, 2006). Further research also revealed that a region in the brainstem was responsible for triggering these so-called locomotor CPG behaviours. This region was later known as mesencephalic locomotor region (MLR) (Duysens and Van de Crommert, 1998). Research showed that stimulation of MLR regions in paralyzed decerebrate cats triggered these patterns, suggesting that these

networks can also function in the absence of descending cortical commands (Jordan et al., 1979). After initiation of locomotor patterns, sensory feedback arrives at the spinal cord with further information about the ongoing movements, which is then projected to motoneurons through reflex pathways under control of the CPGs. This feedback mechanism aids the precise control of the step cycle while conforming with environmental demands, allowing for more flexibility in the functioning of the CPGs (Rossignol, 2006). In particular, Ia afferents from muscle spindles signalling the stretch of hip flexors can trigger a shift to swing phase (McVea et al., 2005), while Ib afferents from Golgi tendon organs (GTO) respond to load and enhance extensor, or anti-gravity, muscle activity during stance phase for balance (Duysens and Van de Crommert, 1998; Donelan and Pearson, 2004; Rossignol, 2006; Kandel, 2013). These proprioception signals are also organized within the spinal cord and relayed through spinocerebellar systems (Bosco and Poppele, 2001; Bosco et al., 2006). Spinocerebellar tracts project sensory information to the cerebellum and are also known as the lowest level of proprioception processing in the nervous system. Neurons within this system were shown to represent limb movement directions and foot position, contributing to limb state estimation (Bosco and Poppele, 2001). Kuo (2002) also proposed an interplay between feedforward CPG and feedback control mechanisms such that the neural oscillators act to minimize the effects of noise in the sensory information to improve performance. Ultimately, spinal and supraspinal networks combine to form a complex organization that allows the nervous system to generate rhythmic locomotor movement via CPGs, which are modified by sensory feedback and descending commands.

In humans, research has also suggested that a similar spinal organization plays a role in the control of rhythmic movements. For instance, evidence for CPG networks in humans were reported in a study with spinal cord injury patients (Dimitrijevic et al., 1998). This study demonstrated that by stimulating the posterior structures of the lumbar spinal cord in these patients, it was possible to elicit step-like muscle activity even in the absence of higher control centers. This evidence further supports the findings of a case study in which a spinal cord injury patient was able to produce alternating muscle activity (Calancie et al., 1994). Subsequently, it was also demonstrated that this locomotor-like muscle activity in both legs could also be elicited by vibrating an antagonist muscle of a suspended leg in healthy humans (Gurfinkel et al., 1998).

Reflex modulation during rhythmic movements in humans is thought to reflect the activity of the CPGs, and both cutaneous and H-reflexes were shown to be phase and task dependent during arm cycling (Zehr and Chua, 2000; Zehr and Kido, 2001; Zehr et al., 2003; Zehr and Duysens, 2004), similar to leg cycling (Ting et al., 1999). These task and phase reflex modulations were also observed during natural arm swing during walking (Zehr and Haridas, 2003). Several researchers have proposed that there is one CPG for each limb in the cat that are interconnected through propriospinal pathways (Miller et al., 1975; Chandler et al., 1984; Duysens and Van de Crommert, 1998), an idea also proposed for humans (Choi and Bastian, 2007; Marigold and Misiąszek, 2009). Interestingly, Baldissera and colleagues (1998) showed that the H-reflex, a monosynaptic spinal-reflex elicited by electrical stimulation, of the flexor carpi radialis muscle in the arm, was modulated and changed with rhythmic flexion-extension foot movements. Furthermore, behavioural responses to perturbations also elicited responses in the arms even when the perturbation was applied elsewhere, such as the lower limbs (Wannier et al., 2001; Marigold and Patla, 2002; Marigold et al., 2003; Misiąszek, 2003). Overall, these results suggest that human arm and leg movements are controlled by complex neural circuitry, which can be mediated by feedback and descending commands. Descending commands from cortical and subcortical levels allow for more independent and voluntary control during reaching and walking.

Many different brain regions have been identified for the control of reaching and walking. In reaching, the posterior parietal cortex (PPC) has been recognized as an area important for movement planning (Snyder et al., 1997; Buneo et al., 2002; Buneo and Andersen, 2006). In particular, goal directed reaching movements require the localization of targets and objects through vision, and localization of the body in space through proprioception to calculate a difference vector between the two. Given that the PPC receives multiple sources of feedback including vision and proprioception, research showed that this area is important for transforming these sensory inputs into a common reference frame for movement planning and online corrections (Kalaska et al., 1983; Snyder et al., 1997; Batista et al., 1999; Desmurget et al., 1999; Pisella et al., 2000; Buneo et al., 2002; Della-Maggiore et al., 2004; Van Der Werf et al., 2010; Vesia et al., 2010; Vesia and Crawford, 2012). Indeed, the PPC is thought to connect to subsequent areas involved in planning and execution of movements (Münchau et al., 2002; Cisek

and Kalaska, 2010). The premotor cortex shows discharges as a function of arm position and research suggests that this area encodes objects with respect to the hand or the difference vectors necessary for the action (Graziano et al., 1997; Mushiake et al., 1997; Schwartz et al., 2004). In addition, neurons in this region are involved in planning the direction of a reaching trajectory (Graziano et al., 1997; Mushiake et al., 1997; Shen and Alexander, 1997; Schwartz et al., 2004; Cisek, 2006; Cisek and Kalaska, 2010). In addition, Freund and Hummelsheim (1985) studied patients with lesions in the premotor cortex and found different patterns of muscle activation of shoulder and hip muscles together with delays of activation of proximal arm muscles. Their results suggest a participation of this area in the control of different movements. This area is also thought to connect to the motor cortex, which in turn is responsible for producing accurate reaching movements (Graziano et al., 2002; Graziano and Aflalo, 2007). In fact, a large body of literature has identified the role of the motor cortex for signaling muscle force and controlling movement trajectory (Kalaska et al., 1989). In addition, the motor cortex has been proposed to have a complex organization that influence aspects of movements or movements with different effectors (Graziano et al., 2002; Meier et al., 2008).

Additionally, the cerebellum plays an important role in the control of movement. Patients with cerebellar damage show a variety of movement abnormalities that affect reaching and arm movements (Bastian, 2011). In particular, cerebellar patients may decompose and perform arm movements in multiple parts, an abnormality known as decomposition of movement (Schweighofer et al., 1998). Often patients exhibit dysmetria, which is an inability to judge distance and scale arm movements to targets and is reflected by irregular, curved and variable movements (Bastian, 2011). In addition, the cerebellum is involved in temporal properties of voluntary movements (Spencer et al., 2003; Ivry and Spencer, 2004). Subsequent studies demonstrated that this region is also involved in estimating muscle force for motor commands of movements (Pasalar et al., 2006; Donchin et al., 2012; Charles et al., 2013). A healthy cerebellum is then fundamental for the control of visually guided movements.

Research, predominantly performed in cats, has demonstrated the use of similar brain regions for the control of visually guided locomotion. For instance, cerebellar neurons discharge in relation to eye movements and stepping over a ladder (Marple-

Horvat et al., 1998) and at different phases of step cycle (Marple-Horvat and Criado, 1999), suggesting a role for this region in coordinating visually guided limb movements during locomotion. This may also explain why cerebellar patients have difficulty adapting to novel sensorimotor relationships after visuomotor perturbations during both reaching and walking (Morton and Bastian, 2004; Donchin et al., 2012). In addition, Lajoie and Drew (2007) found that lesions in the PPC in cat caused errors in the forelimb placement while stepping over an obstacle as well as in the fore and hindlimbs coordination. Area 5 of the PPC revealed increased discharge activity when vision was required to modify gait (Andujar et al., 2010) and during interlimb coordination when estimating the spatial and temporal location of obstacles with respect to the body (Lajoie et al., 2010). These results suggest that the PPC play a role in planning gait modifications (Drew et al., 2008a). Interestingly, recent research in humans demonstrates that different PPC regions encode different effectors, such as for reach and foot movements (Heed et al., 2011; Leoné et al., 2014).

In contrast, research has shown that descending commands from the motor cortex are responsible for movement execution, driving specific changes in gait modifications (Drew, 1988; 1993; Drew et al., 1996; 2002; 2008b; Zabukovec et al., 2013). Drew and collaborators (1996) investigated the role of the motor cortex for locomotion in cats through inactivation of neurons in that region or lesions to the corticospinal tract. Results showed that this area and its related tract regulate muscle activity during gait modifications of limb trajectory. In particular, this area was shown to control groups of muscles and discharge similar to muscle activations to guide the limb over obstacles. Neurons in this area were also shown to discharge more heavily during visually guided locomotion when task precision increased (Beloozerova and Sirota, 1993; Drew et al., 2008a; Drew and Marigold, 2015). More recently, this region was also shown to play a role in the modifications of specific muscle synergies both during changes in gait and reaching in cats (Yakovenko et al., 2011; Krouchev and Drew, 2013). All these supraspinal regions work together and the resultant yields Descending commands arising from these supraspinal regions are subsequently integrated into the circuits of the spinal cord, providing further information for movement control. Specifically, research has indicated that supraspinal descending commands are superimposed onto CPG activity within the spinal cord, driving changes in gait and

allowing for flexible control of movements based on vision and further sensory information (Drew, 1991; Taga, 1995; Krouchev and Drew, 2013).

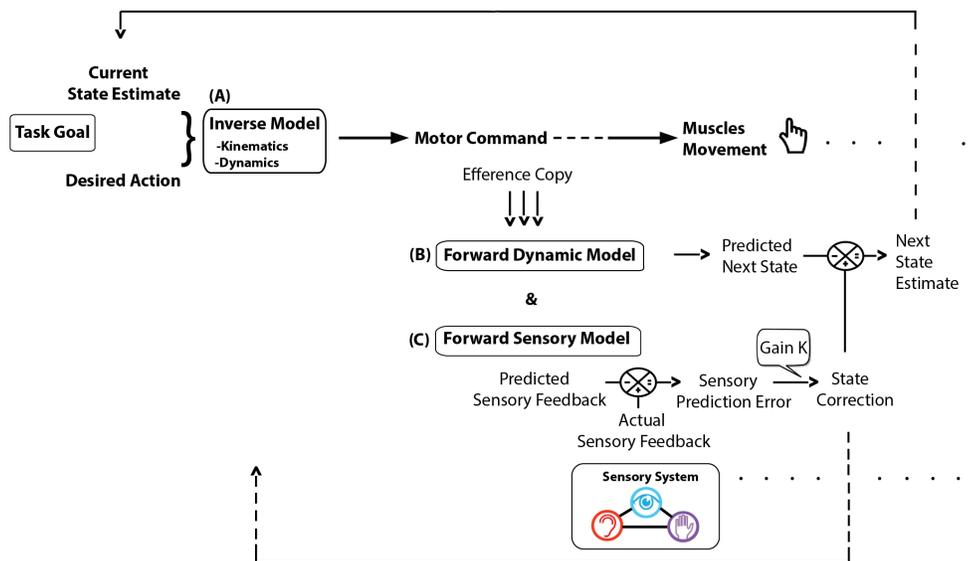
This section shows that reaching and walking require complex interactions between sensory input, cortical, subcortical and spinal levels of control. Some have even suggested that reaching evolved from quadrupedal locomotion (Georgopoulos and Grillner, 1989; Dietz, 2002), with control becoming more specific for the particular effector involved in the movement. Nevertheless, all sensory and motor command signals within the nervous system are limited in terms of their inherent delays and noise. Given this idea, the nervous system is left with the challenge of controlling and guiding arm and legs movements in the face of these sensorimotor uncertainties. The next section focuses on a framework of movement control that has been developed under this perspective.

### **1.3. Internal Models**

Humans have an incredible capacity to adapt and learn movements, and these phenomena have intrigued many scientists over the past several years. The groundbreaking work by Helmholtz (1867), in fact, brought a new way of thinking in the area of neural control of movement when he first introduced the concept of motor predictions. In particular, by gently touching one of his eyes through the eyelid, he observed that an eye movement caused by his touch led to a false perception that the surrounding environment was moving. This observation led to the conclusion that the brain was able to use a copy of its motor commands during self-generated eye movements to predict gaze position and nullify these false perceptions. This idea was then formalized as the concept of efference copy (Holst and Mittelstaedt, 1950), or corollary discharge (Sperry, 1950), which later led to a general framework for motor control, termed internal models (Kawato et al., 1987; Wolpert et al., 1995; Wolpert and Miall, 1996; Jordan and Wolpert, 1999).

Internal models are known as neural circuits that have the ability to perform multiple sensorimotor transformations based on a general understanding of how the body and environment functions. These circuits can be characterized into two main

sections, where each is responsible for controlling a specific aspect of movement (Wolpert and Miall, 1996). The first section is known as the inverse model (Atkeson, 2002; Shadmehr and Wise, 2005), and it is responsible for performing sensory-to-motor transformations, that is, providing the appropriate motor commands to yield the desired action (Figure 1, A). This model can be further subdivided into inverse kinematics and dynamics, which allow the nervous system to calculate a set of joint angles, and to calculate the torques necessary to actually perform the motion given the geometric features of the body, respectively. The second section is known as the forward model and it is further subdivided into forward dynamic and sensory models. Both of these models are responsible for performing motor-to-sensory transformations, calculating the predicted changes in body state (Figure 1, B) and the predicted sensory consequences (Figure 1, C) given a copy of the motor command, respectively (Jordan and Rumelhart, 1992). This framework has shown a potential to explain human sensorimotor control.



**Figure 1. Schematic representation of the internal model framework.**

An inverse model (A) represents the section of the model that calculates the motor commands, which include the appropriate joint parameters (inverse kinematics) and torques (inverse dynamics), based on the desired movement and the current state. A forward dynamic model (B) and a forward sensory model (C) estimate the state and the sensory consequences based on a copy of the motor commands, respectively.

The internal model framework has become the main explanation to several problems in sensorimotor control (Wolpert et al., 1995). For instance, neural signals are temporally delayed and are corrupted by considerable amounts of noise. These delays, which refer to the time taken for the transduction, transport and processing of sensory and motor signals, make real-time monitoring and control of limb state challenging, especially when controlling ballistic movements (Keele and Posner, 1968; Glencross and Koreman, 1979; Zelaznik et al., 1983; McLeod, 1987; Barrett and Glencross, 2001). In addition, the inherent noise in the sensorimotor system can affect how the information is perceived and communicated throughout the nervous system (Harris and Wolpert, 1998; van Beers et al., 2002; Körding and Wolpert, 2006; Faisal et al., 2008). Noise at a cellular level builds as a result of random processes including membrane excitability, ion channel opening/closing, synaptic transmission and neuronal interactions. Sensory noise can be caused by transduction, amplification and processing of multiple sensory signals, and motor noise can change based on noise in the motor commands, motor neurons and muscles involved in a particular action (Faisal et al., 2008). Together, these limitations can cause a great amount of instability and variability during movements under feedback control, such as when trying to intercept a tennis ball moving at 100km/hr. In this case, an internal forward model can provide an estimate of the sensory consequences and limb state in advance, which reduces the need for online sensory feedback and overcomes much of the delays and noise. These predictions also allow for an inverse model to issue the appropriate motor commands on time for fast responses (Wolpert and Miall, 1996).

Another problem of sensorimotor control that can directly affect human behaviour is the problem of distinguishing between sensory signals that originate as a result of environment changes (sensory afference) versus self-generated movements (re-fference) (Wolpert and Miall, 1996; Dokka et al., 2010). For example, the vestibular system provides only subjective information about self-motion due to the fact that it detects head motions that could be a result of self-motion and external perturbations (Cullen, 2012; Massot et al., 2012; Carriot et al., 2013; 2014). Thus, postural control requires the nervous system to distinguish between these two mechanisms. This problem can also be observed when interacting with the environment. For instance, lifting objects in the environment may be perturbed when the weight of objects are

different than expected, thus causing the object to slip between the fingers. Consequently, distinguishing between object and hand motions is fundamental to accommodate the grip aperture properly (Blakemore et al., 1998a; Flanagan et al., 2003). A hallmark of the forward model is that the predicted sensory consequences can be compared with actual sensory feedback to remove self-generated movements from the outcome and to make that distinction (Figure 1, C). The same idea has also been used to explain why we cannot tickle ourselves (Weiskrantz et al., 1971; Blakemore et al., 1998b; 2000) and how eye movements work (Holst and Mittelstaedt, 1950; Sperry, 1950).

Lastly, considering that age, disease and fatigue constantly change the integrity of the musculoskeletal apparatus, and that different environments may change how we move, the mechanisms underlying the control of movements cannot be hard-coded. For example, the nervous system has to be able to adapt movements based on task, body and environment constraints, such as when trying to move different tools with distinct weights and shapes, or move inside a swimming pool in which the movement dynamics change. This leads to a dynamic system problem, in which the states change overtime. In fact, this case may be even more problematic given that each sensory system is captured in its own coordinate system, such as vision, somatosensory, and vestibular (Bizzi et al., 1991; Wolpert, 1997; Jordan and Wolpert, 1999; Pouget and Snyder, 2000; Shadmehr and Wise, 2005). By pairing the predicted sensory consequences with the actual sensory feedback, a forward model yields a sensory prediction error (see Figure 1, C), which is capable of informing how accurate the predictions were and whether there should be any changes in the motor commands in subsequent movements (Jordan and Rumelhart, 1992). As this model is constantly updated, it sheds light on how movements are flexibly controlled over time (Wolpert et al., 1995; Vaziri et al., 2006).

The concept of internal models has grown to cover a wide range of paradigms, including those involving eye movements (Holst and Mittelstaedt, 1950; Sperry, 1950; Chen-Harris et al., 2008; Ethier et al., 2008; Xu-Wilson et al., 2009), reaching in force fields (Brashers-Krug et al., 1996; Donchin et al., 2012), reaching with rotated feedback (Miall et al., 2004; Krakauer et al., 2005), interceptive actions (Kwon and Knill, 2013), and object manipulation (Witney et al., 2000; Flanagan et al., 2001; Ahmed et al., 2008;

Reichelt et al., 2013). Additionally, similar findings have also been shown in paradigms during walking, such as walking on split-belt treadmill (Choi and Bastian, 2007; Torres-Oviedo et al., 2011; Malone et al., 2012), walking with elastic force fields (Noel et al., 2009; Barthélemy et al., 2012; Blanchette et al., 2012), walking with a velocity-dependent resistance (Lam et al., 2006), and walking with altered visual feedback (Morton and Bastian, 2004; Tseng et al., 2010; Alexander et al., 2011; 2013). These studies strongly suggest that the brain uses an internal model to control movements.

Over the past few years, research in patient population, brain stimulation, neuroimaging and single cell recordings in non-human primates have shed light on the neural circuitry underlying the internal models. A few key structures have been identified and suggested to play different roles related to the framework. Research has shown that the cerebellum is involved in state estimation (Paulin et al., 2001; Miall et al., 2007), and that it does so by receiving a copy of the descending motor commands and ascending proprioceptive feedback (Wolpert et al., 1998b; Pasalar et al., 2006; Shadmehr et al., 2010). The cerebellum is also involved in forward sensory predictions, which in turn helps form an ideal circuitry for movement adaptation and learning (Morton and Bastian, 2004; Diedrichsen et al., 2005; Martin et al., 2005; Tseng et al., 2007; Criscimagna-Hemminger et al., 2010; Taylor et al., 2010; Galea et al., 2011; Wiestler et al., 2011; Izawa et al., 2012; Schlerf et al., 2012; Bhanpuri et al., 2013). During inaccurate movements cerebellar-climbing fibers convey information from the inferior olivary nucleus, which responds to movement errors, and reduces the synaptic strength of Purkinje cell activity onto mossy-parallel fiber input (Gilbert and Thach, 1977; Nguyen-Vu et al., 2013; Guo et al., 2014; Yang and Lisberger, 2014). Since Purkinje cells output the cerebellum via the deep cerebellar nuclei to different brainstem and cortical regions, this circuitry may serve as a driving signal for movement corrections. Indeed, different areas of the cerebellum were shown to be active in an fMRI study in humans, when reaching errors were due to a miscalibration of the internal models (Diedrichsen et al., 2005). Additionally, the cerebellum was demonstrated to perform the inverse model calculations, estimating limb's inverse dynamics and force of movements (Pasalar et al., 2006; Donchin et al., 2012; Charles et al., 2013).

The PPC is also known to play an important role in the internal model framework. This region receives abundant sources of feedback related to vision and proprioception and is involved in sensorimotor coordinate transformations, movement planning, rapid online updating and correction of movements (Kalaska et al., 1983; Snyder et al., 1997; Batista et al., 1999; Desmurget et al., 1999; Pisella et al., 2000; Buneo et al., 2002; Della-Maggiore et al., 2004; Grefkes et al., 2004). The PPC is thought to function by estimating the state of movements and feedback (Duhamel et al., 1992; Wolpert et al., 1998a; Buneo et al., 2002; Mulliken et al., 2008a). In particular, it was proposed that the efference copy of motor commands is also sent to parietal regions to eliminate sensory delays and allow for these estimations (Kalaska et al., 1983; Jackson and Husain, 2006; Mulliken et al., 2008b; 2008a). For instance, neurons in the lateral intraparietal cortex (LIP) discharge in advance of even fast saccades to estimate retinal consequences of the eye movements (Duhamel et al., 1992). Given the time consuming delays of sensory feedback, human saccades have been of particular interest to study how the brain maintain and uses internal representations. In this line of reasoning, an additional view of has also indicated that the frontal eye field (FEF) also discharge in advance of eye movements and that a pathways from the superior colliculus to the FEF though mediodorsal thalamus is responsible for providing the efference copy to estimate eye position during eye movements (Sommer and Wurtz, 2002; 2004a; 2004b).

In addition, Mulliken et al. (2008b) demonstrated the role of the PPC in state estimation related to goal-directed reaching movements. They recorded from PPC neurons while a monkey moved a cursor on the screen to a target. They found that the discharge activity of many PPC neurons was correlated with the current movement angle, reflecting a forward estimate of the movement. These results of state estimation in the PPC agree with a reported case study of a patient with a lesion in the superior parietal lobe who exhibited deficits that reflected an inability to maintain a representation of limb state (Wolpert et al., 1998a).

Another function of the PPC that links this region with the functioning of the internal models is that this region is also involved in detecting movement errors. For instance, neural activity in this area was modulated during reach movements as a function of errors in the dark (MacKay, 1992). In addition, a decreased  $\beta$  event-related

synchronization in this area with respect to reaching movements has also been proposed to reflect neural mechanisms that evaluate errors (Tan et al., 2014). The PPC was also shown to be largely active during visuomotor rotation paradigms that create to an error reduction process during the adaptation phase (Inoue et al., 2000; Culham et al., 2006; Girgenrath et al., 2008).

Desmurget and colleagues (2001), using positron emission tomography (PET), observed different modulation of the PPC, cerebellum and the motor cortex, when subjects made corrections in a visuomotor pointing task. Together with their results, they proposed that the PPC was responsible for computing motor errors and communicating it to the cerebellum. In addition, given that they observed a co-activation of the pre-central gyrus with cerebellar areas they proposed that the cerebellum receives those error signals and make appropriate changes in the motor commands from the primary motor cortex. Further evidence of brain activation of the PPC and cerebellum also support the notion that these areas together may be involved in the error reduction process of adaptation (Krakauer et al., 2004; Graydon et al., 2005; Newport and Jackson, 2006; Danckert et al., 2008; Luauté et al., 2009; Chapman et al., 2010; Bédard and Sanes, 2014).

Despite advances in the literature towards identifying the neuronal networks of the internal forward and inverse models, it is still largely unknown how these different areas function together in different experimental paradigms. The next section focuses on how paradigms using visuomotor behaviour can help us understand how movements are controlled.

## **1.4. Visuomotor Adaptation**

Visually guided movements to targets or objects can happen in a way that is not in consonance with the time taken for sensory feedback to become available. Thus, in order to perform movements, the brain is required to maintain an internal representation or a relationship between perceived spatial locations and motor commands required to achieve the goal (i.e., a visuomotor mapping) (Shadmehr et al., 2010). Over the course of life, this visuomotor mapping can change as a result of new prescription glasses, eye

disease, or through the use of interactive computers, causing movement errors and forcing the brain to adapt. Movement errors as feedback, can inform the nervous system that the outcome of its previous action did not match the predicted or expected action, leading to sensory prediction error that can drive adaptation. In this context, visuomotor adaptation serves to update the predictions and reduce these movement errors by compensating for the altered visual conditions to return to a previous standard of performance. This process of adaptation does not require learning of new patterns of muscle activation or a specific skill, but rather learning a new visuomotor mapping. For instance, when learning how to move a mouse on the screen set at a different gain of speed, a new visuomotor mapping should be established to link the arm movements with the new speed of the cursor. Subsequent exposures to these altered conditions may lead to consolidation of motor memories, facilitating subsequent exposures to perturbations of similar nature (Krakauer et al., 2005). The study of how we adapt and learn new visuomotor mappings has yielded significant insight for understanding the framework of internal models during the control of movements.

In the laboratory, it is possible to study this process of visuomotor adaptation by artificially disrupting the normal visuomotor mapping, either by rotating visual feedback (Krakauer et al., 2005; Mazzoni and Krakauer, 2006; Krakauer, 2009; Taylor et al., 2014) or by shifting visual perception with prism glasses (Redding and Wallace, 2003a; 2003b; Morton and Bastian, 2004; Redding and Wallace, 2006a; 2010). These techniques yield movement errors, and cause sensory prediction errors interpreted as a mismatch between predicted and actual sensory feedback. When the rotated or shifted feedback is removed, movements overshoot a target to the opposite side, indicating that a new visuomotor mapping was established (Redding and Wallace, 2006a). These paradigms can also result in visual, proprioceptive and motor recalibration by inducing an adjustment of the felt position of the eye, limb and the motor commands, respectively (Cunningham and Welch, 1994; Morton and Bastian, 2004; Henriques and Cressman, 2012). A fundamental difference between these paradigms is that the visuomotor rotation paradigm requires a screen to virtually project and rotate the feedback while prism glasses are mobile and extend the range of tasks that can be studied.

The principles underlying visuomotor adaptation originated mainly from reaching paradigms with visuomotor rotation and prism glasses (Harris, 1965; Redding and Wallace, 1985; 1988; 2001; 2003a; 2003b; Martin et al., 2005; Redding et al., 2005; Redding and Wallace, 2006b; 2006a). More recently, studies suggest that the nervous system adapts human locomotion in a similar fashion (Harris and Carré, 2001; Morton and Bastian, 2004; Michel et al., 2008; Errington et al., 2013). In particular, research indicates that humans adapt locomotor trajectory (Kennedy et al., 2003; Morton and Bastian, 2004; Michel et al., 2008; Ito et al., 2010) and foot placement errors in a precision walking and an obstacle avoidance task (Alexander et al., 2011; 2013) over repeated attempts with prism exposure. Taken together, these results support the notion that the nervous system is capable of reducing sensory prediction errors similarly in different tasks.

Additional evidence for how the nervous system controls different classes of movements may lie in generalization studies (Shadmehr, 2004). Generalization studies ask how much the predictions from an internal model transfer to other contexts, thus providing important information on how adaptation is encoded across tasks (Shadmehr and Moussavi, 2000; Pearson et al., 2010). For instance, Martin et al. (2005) found limited generalization following prism adaptation across different throwing trajectories and arms. This and subsequent findings support the notion that adaptation might be context specific (Taylor and Ivry, 2013), and also a function of the statistics of previous practice (Krakauer et al., 2006). These different generalization profiles during arm movements were also explained by the fact that these internal representations might not only compensate for motor errors, but also estimate the source of errors (Berniker and Körding, 2008). In the context of walking, Alexander et al. (2011; 2013) reported broader, but asymmetric, generalization across different walking tasks. In addition, Morton and Bastian (2004) found broad generalization from walking to reaching, but not from reaching to walking. Opposite findings have also been reported by Michel et al. (2008) and Savin and Morton (2007), in which only arm pointing movements generalized to leg or walking trajectory, respectively. Together, these differences in generalization profiles suggest that the characteristics of the tasks, possibly their demands in terms of control of degrees of freedom, might dictate how predictions can be used to update motor commands across a variety of tasks.

This section provided the basis for visuomotor control in the performance of different classes of movements. However, a limitation in the proposed internal model framework is that all movements happen in presence of large amounts of uncertainty. Thus, the computations performed by the brain may not be as straightforward as has been proposed. Next, I will approach the role of uncertainty for sensorimotor control.

## **1.5. Uncertainty**

All human movements are inherently uncertain. The nervous system is constantly confronted with the problem that a vast amount of uncertainty arises at all levels of sensorimotor control. From noise corrupting the neural signals to sensory limitations and environmental instabilities, uncertainty accrues and poses a problem to the selection of appropriate motor commands for specific actions. Thus, understanding the causes and effects of uncertainty in the nervous system may provide clues to how movements are controlled.

One source of uncertainty stems from the presence of noise in the nervous system. First, noise may build as a result of random cellular processes, including membrane excitability, ion channel opening/closing, synaptic transmission and neuronal interactions, which in turn affect the timing of action potentials even when identical time synchronized stimuli are repeated over trials (van Beers et al., 2002; Faisal et al., 2008). In addition, sensory noise is caused by transduction and amplification of multiple sensory signals. For example, consider the problem of reaching to a juice carton in the middle of the night under dim lighting. In this context, vision is faced with the problem that photons arrive at photoreceptors of the retina at different rates and are absorbed based on the amount of light available, which considerably limits contrast sensitivity (Bialek, 2006). Additionally, motor noise changes based on motor neurons and muscles involved in a particular action. For instance, when the motor commands are sent to move the arm to targets at different distances or objects of different weights, additional amounts of noise are added as a function of the size of the motor commands, causing movement variability with respect to the outcome of the desired action (Harris and Wolpert, 1998; van Beers et al., 2004; Sternad et al., 2011).

An additional source of uncertainty for sensorimotor control is that all sensory receptors have a very limited spatial and/or temporal resolution (van Beers et al., 2002). For example, if vision and proprioception can be used to localize body state, vision is less precise when judging distance, while proprioception is less precise with increasing the distance from the shoulder (Foley and Held, 1972; van Beers et al., 1998; Brown et al., 2003). Thus, the reliability of the information provided by each sensory receptor may change depending on the context. Sensory perception is also limited by the nature of each receptor and how they capture information. For instance, the first stage of vision is to project a 3-dimensional world onto a 2-dimensional retina. This makes the stimulus inherently ambiguous and limits sensory interpretation (Helmholtz, 1867; Yuille and Kersten, 2006; Wolpert, 2007).

Another limitation that contributes and increases the level of uncertainty is that the environment in which we live in is highly unpredictable. When reaching to the juice carton, it is not possible to know whether it is full, empty or half empty, which impairs our ability to select the most appropriate motor commands to lift it (Braun et al., 2009). The multitude of sources of uncertainty can increase movement variability and directly affect the predictions generated by internal models. To investigate this idea, Izawa and Shadmehr (2008) manipulated feedback uncertainty by increasing the blur of a target and asked subjects to reach while compensating for occasional jumps of the target. Results showed that uncertainty affected the estimation of the future target locations, which in turn affected corrections to the jump trials, suggesting that this estimate of the target position would be combined only gradually with sensory evidence on the basis of its uncertainty. This change in the reliability of sensory evidence on the basis of uncertainty also brings the question of whether uncertainty or different types of uncertainty would modulate movement adaptation. Using this line of reasoning, Wei and Körding (2010) investigated the effects of different types of uncertainty on the trial-by-trial adaptation of reaching movements to random visual perturbations. In particular, they increased feedback or state estimation uncertainty by either blurring the feedback or asking participants to stay idle in the dark, respectively. Results showed distinct adaptation rates for each uncertainty condition. Subjects adapted slower with increasing feedback uncertainty and adapted faster with increasing state estimation uncertainty. Wei and Körding (2010) argued that these differences were based on assigning

reliabilities to error feedback information and predictions based on past knowledge over the course of the experiment. In a condition with high feedback uncertainty, participants had to rely more on their predictions, as their feedback did not provide enough information about their outcome. This slowed movement adaptation. On the other hand, in a condition with high state estimation uncertainty, the nervous system had to rely more on feedback than its predictions to guide movements, which then increased the rate of adaptation.

Additional effects of uncertainty were also investigated with perturbations of different nature (Scheidt et al., 2001; van Beers, 2007; Braun et al., 2009; Wei et al., 2010), suggesting that uncertainty modulates movement adaptation. Burge and colleagues (2008) proposed that behavioural responses in the face of uncertainty were due to the fact that the nervous system had to distinguish the actual cause of the movement errors, which then dictates the compensation strategies. For example, a particular movement error could be caused simply because the sensorimotor signals are noisy (measurement noise) or as a result of a misalignment (systematic noise), or both. Measurement noise does not require an update of the predictions from an internal model because movements are variable, but on average are still accurate around the expected outcome. In this case, if the nervous system attempts to update its internal representations movement variability would drastically increase, dragging movements away from the average estimated location on a trial-by-trial basis. Conversely, systematic noise is an indication that there is a bias between the internal representations and movements, and requires an update of a visual estimate of the target and the motor command required to arrive at it. In this case, subsequent movements should then compensate and attempt to bring movement errors to zero to improve accuracy and to establish a new visuomotor relationship.

Considering that movements are inherently variable due to noise, delays in sensory processing, and disease, the nervous system is always faced with the problem of having both sources happening at the same time. Thus, when recalibration is required, movement errors that would inform the nervous system that there is a potential bias of its internal representations are also variable and the amounts of noise may dictate systematically how the nervous system use those errors to adapt. Additional

studies further identified that motor adaptation requires the nervous system to identify the causes of the errors (Berniker and Körding, 2008; Wei and Körding, 2009). In statistics, this phenomenon is also known as the bias-variance trade-off.

Wei and Körding (2009) proposed that the nervous system should adapt based on task relevance. They created a condition in which subjects had to perform reaching movements with randomly displaced visual feedback ( $\pm 8$ ,  $\pm 4$ ,  $\pm 2$ ,  $\pm 1$  and  $0$ cm). Results showed that subjects approached the high displacement perturbations as being caused by external events and thus, adapted instead to the values closer to the center of the distribution of perturbations. Using a similar experimental paradigm, Wilke et al. (2013) further identified that adaptation happens when the value of errors is attributed to internal or more relevant causes. Together, these results suggest that since external events have a low probability of occurrence, such as in the case of a sudden perturbation of a gust of wind, any motor adaptations to those perturbations would decrease the performance and lead to overcompensations in subsequent movements. On the other hand, events that have higher probability of occurrence are more relevant and need corrections to improve subsequent movements.

The experimental results presented in this section show that the nervous system controls movement in the face of large amounts of uncertainty. Since uncertainty arises from everywhere, the best guess might be to estimate variables that are relevant and that occur more often, which implies that the nervous system needs to consider prior experiences when performing these estimations. Mathematical models can be used to confirm these predictions.

## **1.6. Computational Models**

Mathematical models can be used to provide important insights into the computations performed by the brain that govern a specific behaviour. Thus, motor adaptation paradigms are commonly used to form and assess computational models. In particular, a point of interest for modeling is that movement errors tend to decline exponentially across trials. This suggests that motor adaptation is a process that attempts to reduce movement errors as a proportion of the error size, which led to the

creation of state-space model of this process (Thoroughman and Shadmehr, 2000; Baddeley et al., 2003; Donchin et al., 2003; Cheng and Sabes, 2006; Fine and Thoroughman, 2007; Wei and Körding, 2010). For instance, in a reaching paradigm in which the goal of the task is to reach to a target and a visuomotor perturbation is applied by rotating the visual feedback, movement errors ( $e$ ) are a combination of the previous action ( $u$ ) and the perturbation ( $p$ ):  $e = u + p$ . Thus, the state space assumes that subjects adapt their reaching angle or trajectory on subsequent trials to a proportion of the error on the current trial, such as  $u_{k+1} = A u_k + \Upsilon e_k$ . In this case,  $u_{k+1}$  is the estimated hand position, and it is linearly dependent on the previous trial  $u_k$  and the error feedback  $e_k$ . In addition,  $\Upsilon$  determines the fraction of the error that is considered and  $A$  refers to the forgetting rate, as there is a natural tendency to return to baseline state even in the absence of errors (Galea et al., 2011). Importantly, this forgetting rate suggests that adaptation cannot simply reduce errors to zero but the asymptote should be reached at equilibrium between forgetting and adaptation rates based on residual errors.

A state-space model provides a fundamental technique to estimate the adaptation rate and replicate human behaviour in the face of perturbations. This model attempts to describe the process of trial-to-trial error reduction and approaches movement errors equally across trials, suggesting that all movement errors should have a reduction rate associated with it. This trial-to-trial error reduction over time reveals that there are two phases of learning. One phase shows smaller responses to errors and retention and the other that shows strong responses to errors but poor retention. As a result, error reduction curves are better represented by two exponentials with distinct time constants, one fast and the other slow (Smith et al., 2006). In addition, it is possible to define this phenomenon within the state-space model by comprising two components that learn from the same error with different timescales. The component that learns fast also forgets fast, and the component that learns slowly also forgets slowly (Smith et al., 2006). Overall, this two-state model predicts a spontaneous recovery of a previous internal model following rapid adaptation and de-adaptation even in the absence of errors, as well as long term retention and anterograde interference of motor memories (Smith et al., 2006; Joiner and Smith, 2008; Sing and Smith, 2010). More recently,

different state space models with different timescales have also been proposed for prism adaptation (Inoue et al., 2015).

In contrast to state-space models, Korenberg and Ghahramani (2002) suggested that motor adaptation and learning instead should be treated as an inference problem from noisy observations. The key difference here is that the adaptation rate is not an arbitrary parameter, as defined in the state-space model, but it is suggested to emerge given the statistics of the task and its incorporated uncertainty. This idea also indicates that probabilistic models could be used to represent motor adaptation. In particular, a probabilistic model in sensorimotor control proposes that all sensory evidence should be combined with prior experiences in a Bayesian way (Körding and Wolpert, 2004; Berniker and Körding, 2009; 2011a). Bayesian theory, which is a largely known theory in statistics, can reproduce human behaviour in a variety of tasks.

Bayesian theory was first reported in 1764, posthumously, based on the work of an English Presbyterian minister, Thomas Bayes. After his death, one of his friends found a major mathematical proof among one of his papers and published it as an “Essay towards solving a problem in the doctrine of chances” (Bayes, 1984). By the end of the 20<sup>th</sup> century, this idea became one of the pillars of modern statistics, yielding many implications in a variety of areas, including neuroscience (Körding and Wolpert, 2004; 2006; Vilares and Körding, 2011; Berniker and Körding, 2011a). A Bayesian approach in neuroscience is a probabilistic approach that is based on the fact that the nervous system combines different pieces of evidence in the form of sensory information, such as vision, vestibular and proprioception to estimate state variables, such as body, limbs and environment positions. Since the sensory signals are inherently uncertain, it is possible to ask what is the probability of observing that specific data given the sensory information.

Consider the problem of localizing an object (“ $\mathcal{O}$ ”) in space based on two sensory streams, such as vision (“ $S_v$ ”) and proprioception (“ $S_p$ ”). If each sensory stream contains the true location of the object with a measurement of noise, then the most reasonable thing to do is to combine those two pieces of information to get a better estimate of the location of the object. In this case, the noise is assumed to be random and that it would

fall within a normal distribution centered on a zero mean and with a variance based on the quality of the sensors. This idea is also known as maximum likelihood integration and can be represented by the combined probability of observing the object given the two sensors  $p(\mathbb{O}|Sv) p(\mathbb{O}|Sp)$ . To consider the noise in each sensory system, this integration weighs each sensory system inversely proportional to their variances. Thus, the reliability of a sensor would decrease by increasing its variance. This is represented by  $\chi Sv + (1 - \chi)Sp$ , where  $\chi = \frac{\sigma_2^2}{(\sigma_1^2 + \sigma_2^2)}$ . An important point is that the variance of the combined estimate  $\frac{\sigma_1^2 \sigma_2^2}{(\sigma_1^2 + \sigma_2^2)}$  is smaller than the variance of each sensory system individually. This combined probability rule of the sensory systems is used to represent how human combine cues in a statistically optimal fashion (Jacobs, 1999; Ernst and Banks, 2002; Ernst and Bühlhoff, 2004). Nevertheless, the main point of interest is still to compute the location of the true parameter “O”, and this cannot be explained simply by sensory feedback.

Since sensory feedback can be further compared with their predicted consequences based on the knowledge of the motor commands and also a general understanding of the physics and the body, the models of sensorimotor control should combine the sensory likelihood with experiences over time. This simple, intuitive, but rather powerful idea, is the core of Bayesian theory. Bayes rule proposes that the sensory *likelihood*  $P(S|\mathbb{O})$  can be combined with *prior* experiences  $p(\mathbb{O})$ , which is the probability of the parameter without a bias from any current sensory evidence (Beierholm et al., 2009), to further improve the estimate of the location of the object  $P(\mathbb{O} | S)$ . Given that uncertainty increases variability, the key point of this approach is that this estimation, or posterior,  $P(\mathbb{O} | S)$ , is a probability based on the variability of the sensors and prior experiences, which both are reduced in combination. This probability is normalized by the probability of the sensory feedback  $p(S)$ , which is based on their variances to yield a probability between 0-1.

$$P(\mathbb{O}|S) = \frac{P(S|\mathbb{O}) p(\mathbb{O})}{p(S)}$$

Models of Bayesian have been demonstrated in a number of human behaviours such as force estimation (Körding et al., 2004), reaching (Körding and Wolpert, 2004; Burge et al., 2008; Brouwer and Knill, 2009), pointing (Tassinari et al., 2006), movement timing (Miyazaki et al., 2005), interceptive actions (Kwon and Knill, 2013; Narain et al., 2013), and eye movements (Najemnik and Geisler, 2005). This research demonstrates that subjects can efficiently use prior experience to improve performance.

A recursive Bayesian estimation model, also known as the Kalman Filter (Kalman, 1960) can address the problem of updating those priors over time to improve the estimation. This approach is largely used as a system identification tool in the face of noisy and missing data, such as in the case of tracking targets, aircrafts, robots and interactive maps. This model combines noisy observation with prior knowledge in a specified proportion (Kalman gain) over time in a way that the posterior probability is updated when new information is available. The Kalman gain is a function of the measurement noise from the sensors and systematic noise from external processes and can define how sensitive the model is for changes.

Additional experimental evidence moved to identify what strategies and computations the brain performs when adapting. In particular, Baddeley and collaborators (2003) asked subjects to perform pointing movements to targets and manipulated the visuomotor mapping (feedback and actual pointing movement) randomly with increasing measurement noise in conditions with and without vision. They proposed that conditions where uncertainty about the hand location with respect to cursor increases, performance was impaired by action noise. A Kalman filter model was similar to the behaviour in this protocol, suggesting that the nervous system might implements similar filters to estimate and adapt visuomotor mappings.

Burge and colleagues (2008) further manipulated observation noise (feedback uncertainty) and a systematic noise (visuomotor mapping uncertainty) in a reaching paradigm. The systematic noise forced the nervous system to adapt to compensate for the subtle and constant changes in the visuomotor mapping. Conversely, the observation noise confounded the nervous system, as in this case it did not require the implementation of a strategy to compensate for a new mapping. The predictions were

twofold. First, increasing the observation noise should lead to a decrease in the sensitivity to errors (the nervous system should not trust the errors). Second, increasing the systematic noise should lead to an increase in the sensitivity to errors (the nervous system should trust and adapt to the errors). Results showed that the adaptation rates in those conditions followed these predictions and were slower with increasing observation noise. In addition, the Kalman gain accurately predicted and scaled the adaptation rates based on those predictions. Other models based on Kalman filter were shown to be similar to the behavioural responses, which supports the need to take uncertainty into account for movement adaptation (Wei and Körding, 2010; Marko et al., 2012; Yamamoto and Ando, 2012).

Recently, Stevenson and others (2009) investigated whether those principles would also hold in case of more complex movements. In particular, participants were asked to steer a cursor on the screen by shifting their center of pressure while balancing on a surfboard. Feedback uncertainty was manipulated by blurring the cursor on the screen. Results showed that subjects integrated information over time and considered the levels of uncertainty. However, the behavioural responses were limited given the tasks high biomechanical constraints.

The mechanisms behind how priors are adaptable and function for multiple tasks, as well as the neural mechanisms underlying the adaptive behaviour are still unclear. This project aims at determining the effects of sensorimotor uncertainty during adaptive locomotion.

## **1.7. Research Aims and Hypotheses**

Evidence suggests that the neural control of upper and lower limbs may share a common framework, and utilize similar brain regions. A large body of research has studied upper limb reaching movements to understand how the nervous system deals with the problem of uncertainty when adapting to perturbations. In this study, **our objective was to experimentally determine how the nervous system adapts in the face of sensorimotor uncertainty during visually guided walking.**

This thesis provides new insights into how the sensorimotor system deals with uncertainty to control and adapt human walking. Identifying the strategies for visuomotor adaptation in the face of uncertainty will provide a better understanding of the factors and stimulus properties that determine human adaptation rates. This is important for better estimating the recovery rates when manipulating sensory experiences in a rehabilitation environment. Additionally, the study of motor adaptation in different contexts with different effectors expands our current view and theories of motor control and learning, and reveals new insights into how the nervous system works to control movement.

### **1.7.1. Specific Aims**

***To determine how increasing sensorimotor uncertainty affects visuomotor adaptation during walking.***

To accomplish our goal, subjects performed a precision walking task that required them to walk across a 6m walkway and step with the right foot onto a single target (36 x 3 cm) without stopping. We altered the subject's visuomotor mapping in the adaptation phase of each protocol using prism goggles that displaced the perceived target location of the target that they had to step on. To this end, we changed the mean prism shift to 18 diopters (10.3 degrees) in the adaptation phase from a mean of 0 diopters (0 degrees) in a baseline phase, and thus requiring subjects to adapt over repeated trials by recalibrating the visuomotor mapping. We simulated uncertainty (referred to as noise) in the visuomotor information by varying the strength and direction of prismatic shifts around these mean values, on a trial-by-trial basis. The strength and direction were varied using a Gaussian distribution for each baseline and adaptation phases of the protocol. The range of the distributions, either 0, 12 or 24 diopters (0, 6.7, 13.7 degrees), defined the no, low and high noise conditions, respectively.

### **1.7.2. Hypothesis**

Previous research has shown that the nervous system weights feedback uncertainty with prior experiences during adaptation to visuomotor perturbations (Wei and Körding, 2010) and uses an internal model for the control of visually guided walking tasks (Morton and Bastian, 2004; Alexander et al., 2011; 2013). Thus, we hypothesized that the control of precision walking relies on a combination between predicted and actual sensory feedback according to their respective reliabilities. In particular, based on previous results (Burge et al., 2008; Wei and Körding, 2010), we hypothesized that by increasing error feedback uncertainty, movement variability will increase, and the nervous system becomes less sensitive to errors, adapting more slowly to a systematic change in the prismatic shifts. Error sensitivity reflects uncertainty because it would inform the system that any motor compensation to random errors would instead deteriorate performance. This is also evidence that individuals decrease the weight of the unreliable error information and increase their reliance on prior experiences when estimating uncertain variables. Thus, we hypothesized that this weighting of prior experiences also makes the system less affected by visuomotor perturbations.

## **Chapter 2. The Role of Sensorimotor Uncertainty in Visuomotor Adaptation During Walking**

### **2.1. Introduction**

Locomotion and reaching behaviours have long been treated as distinct motor tasks. Previous research has predominantly studied human locomotion from the perspective that its control is dominated by reflexive, pattern generating, and balancing circuits located in the spinal cord and brainstem (Rossignol, 2006). Conversely, studies in reaching have instead considered that the precise and ballistic nature of arm movements require higher-level cortical control (Desmurget et al., 1999; Diedrichsen et al., 2005). Despite these differences, it is hypothesized that reaching likely evolved from quadrupedal locomotion (Georgopoulos and Grillner, 1989; Dietz, 2002). Over the course of evolution, humans evolved to use bipedal locomotion and developed more specialized hand functions, such as reaching and grasping. Both of these abilities require higher demands of precision in the control of each limb, and these are thought to involve complex feedback control. In particular, as a multitude of sensory feedback arises, a weighting of vision and proprioception sensory feedback is important for localizing the limb's state (Sober and Sabes, 2005; Marigold, 2008). In addition, visual feedback is also important for localizing the targets in the environment, such as a cup of coffee for reaching, or a stepping-stone for walking. All sensory information then needs to be converted into coordinates appropriate for movement, which entails computing a difference vector (distance) between the location of the target and limbs (Shadmehr and Wise, 2005). This suggests that similar mechanisms might be used in the planning stages of goal directed limb movements.

Over the past years, however, research has largely shown that goal directed arm movements are not entirely based on the use of feedback per se. It is also recognized that two constraints of the sensorimotor system limit the efficacy of feedback-based

control. Delays and noise within sensory feedback and motor command signals both create uncertainty and movement variability. In lieu of these ideas, it was proposed that the brain also maintains an internal representation or a mapping between the perceived target location and the motor command to arrive at it (Shadmehr and Mussa-Ivaldi, 1994). This visuomotor mapping helps overcome the limitations of sensory feedback by allowing the brain to estimate their values and consequences, improving the control of smooth and ballistic movements (Shadmehr et al., 2010). A framework called internal models has been developed under this idea demonstrating that humans combine predictions with feedback to improve how they detect their state and control movements accordingly (Shadmehr and Mussa-Ivaldi, 1994; Wolpert et al., 1995). To probe this idea, a number of studies have used perturbation paradigms such as force fields (Shadmehr et al., 2010) or visuomotor rotations (Krakauer, 2009) that can cause a mismatch between these predictions and their actual sensory feedback. These perturbations cause movement errors, and force the brain to adapt. This framework proposes that the brain adapts by estimating new motor commands that compensate for perturbations, reducing movement errors. When subjects attempt to return to the non-perturbed state, large aftereffects are observed, which have been considered as evidence that humans adapt according to this framework (Shadmehr and Mussa-Ivaldi, 1994; Krakauer, 2009).

More recently, research has shown that humans also adapt to visuomotor perturbations during precision walking, and strong aftereffects are observed following an adaptation period (Morton and Bastian, 2004; Alexander et al., 2011; 2013). Similar to reaching movements, these researchers proposed that motor adaptation results from constant comparisons between expected and actual feedback. A major limitation to this process, however, is that sensory feedback in a biological system is largely imperfect which in turn affects how the nervous system might interpret and use movement error feedback (van Beers et al., 2002; Faisal et al., 2008). Thus, the nervous system is left with the problem of dealing with ambiguous movement errors to improve movement accuracy both in visually guided reaching and walking.

Burge and colleagues (2008) proposed that when a motor command is issued in a goal directed movement and an error is observed, this error feedback could be the

result of a miscalibration, random sensorimotor noise in the nervous system, or a combination of both. A miscalibration creates a bias between the internal visuomotor mapping and movements. This requires the use of movement error on a movement-by-movement basis to update of the visual estimate of the target and the motor commands required to accurately reach it. Conversely, random sensorimotor noise corrupts all sensory input and motor output signals in the nervous system, which in turn leads to an increase in movement error variability despite the fact that the average outcome is essentially within the estimated location. In this case, if the nervous system attempts to compensate and reduce movement errors to zero, movement variability would instead drastically increase. Thus, errors of this cause require ignoring the most recent movement in favour of the history of past movements. Given that sensorimotor signals are inherently noisy, and that the amount of noise may change with age, disease, and size of the motor commands, any perturbation to the normal visuomotor mapping that requires recalibration happens in the face of random amounts of noise and variability. Research in reaching movements has shown that an optimal strategy would require the brain to consider previous trials to make the nervous system less sensitive to random movement errors (Burge et al., 2008; Wei and Körding, 2009; 2010; Berniker and Körding, 2011b; Marko et al., 2012; Wilke et al., 2013). Indeed, adaptation to visuomotor perturbations happen as a function of a weighting between predictions and the reliabilities of sensory feedback (Burge et al., 2008; Wei and Körding, 2010). These studies increased feedback uncertainty by blurring the hand location displayed on a computer monitor, and reported that adaptation to visuomotor perturbations in reaching were based on uncertainty.

Although a similar process of error reduction between reaching and walking may exist (Morton and Bastian, 2004; Shadmehr et al., 2010; Alexander et al., 2011; 2013), it is not clear how the nervous system integrates expectancies and reliabilities of error feedback to adapt visually guided walking. We sought to answer this question and designed an experiment that aimed at determining how the nervous system adapts to visuomotor perturbations in the face of sensorimotor uncertainty during walking. Specifically, we asked whether motor adaptation during walking is sensitive to increasing sensorimotor uncertainty. To test these ideas, we asked subjects to walk and step on a target in the middle of a walkway, while wearing prism goggles that shifted the visual

perception of the target with respect to its actual location. We created a visual miscalibration requiring adaptation by changing the mean prism shift for each phase (baseline, adaptation, and post-adaptation) of the protocol. We manipulated sensorimotor uncertainty (referred to as noise) by varying the strength and perturbation direction of prism lenses on a trial-by-trial basis and created three conditions with distinct distributions around these mean shifts: no, low and high noise. If sensorimotor uncertainty modulates the weighting in which error feedback is used in visuomotor adaptation during walking, then we should expect slower adaptation rates and smaller error initial error amplitudes in the adaptation phase when increasing sensorimotor uncertainty.

## **2.2. Methods**

### **2.2.1. Subjects**

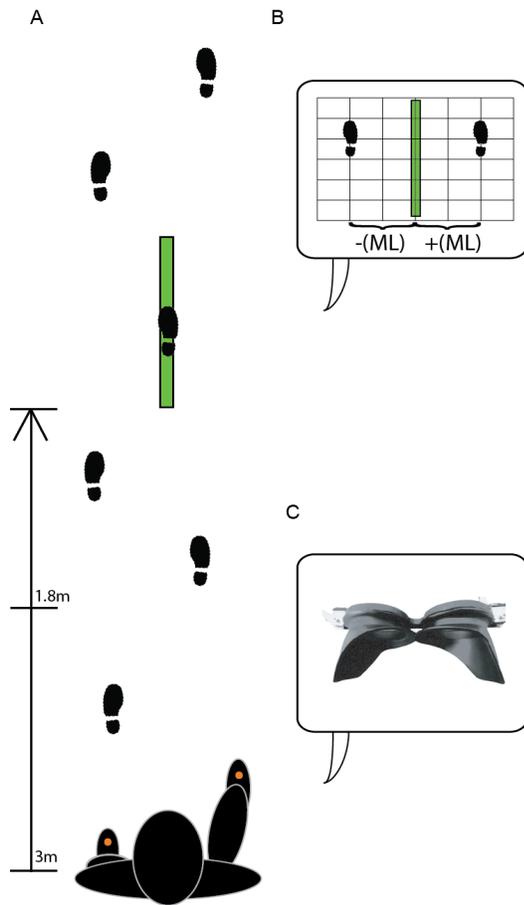
A total of 24 subjects (age =  $21.8 \pm 2.8$  years; height =  $172.9 \pm 9.9$  cm; weight =  $69.9 \pm 11.7$  kg; 15 males and 9 females) with no known musculoskeletal, neurological, or visual disease were recruited from Simon Fraser University to participate in this study. Subjects wore corrective lenses (glasses or contacts) during the experiments, if required (6 subjects). Subject's leg dominance was defined as the dominant leg to kick a soccer ball, and right leg dominance was reported in 21/24 subjects. The Office of Research Ethics at Simon Fraser University approved all experimental procedures for this project, and all subjects gave an informed written consent before participating.

### **2.2.2. Experimental Task**

Subjects were asked to perform a modified limb-based precision-walking task (Alexander et al., 2011; 2013) that was characterized by having to walk across a 6m walkway and step with the right foot onto the medial-lateral (ML) center of one target (36 x 3 cm), without stopping. The target was projected on the ground from above with a projector (Epson EX7200). The length of the target reduced the accuracy demand in the antero-posterior dimension to prevent subjects from using shuffle steps near the target area. Figure 2A illustrates the experimental set-up. The subject's starting location was

randomized between 1.8 and 3m from the target in all trials, except for the first trial of each phase of the protocol, which was fixed at 1.8m from the target. This helped to avoid learning a specific stepping sequence and increased the visual demand of the task. This walking task was designed to involve only a few fast steps to be closer to ballistic reaching experiments while preventing online corrections. The task was performed under a series of dim LED lights that reduced the room lighting at floor level to ~0.7 lux, as measured with a calibrated digital light meter (DML-2200; Circuit Test Electronics, Burnaby, BC). This diminished environmental references and increased the contrast of the projected target.

To study adaptation, we used prism glasses that shifted the visual perception of the target with respect to its actual location. This disrupted the normal visuomotor mapping and induced movement errors after walking and stepping to the perceived location of the target. By manipulating the mean shift of the visual perception during a set of trials, while randomly changing lenses around this constant mean, we studied how subjects adapted in the face of sensorimotor uncertainty. The magnitude and direction of this visuomotor perturbation was manipulated by changing lenses with different degrees of prism shifts and orientations that were attached to goggles (Figure 2C). These goggles reduced a portion of the visual field such that they forced the subjects to look only through the lenses.



**Figure 2. Experimental set-up, measures and equipment.**

Experimental set up: Schematic representation of the precision walking task. Subjects were instructed to walk and step in the ML center of the target with the right foot (Figure 2A). Figure 2 B illustrates the lateral foot placement error measurement. Positive ML values represent end-point errors of foot placement to the right side of the target and negative ML values represent end-point errors to the left side of the target. Figure 2 C illustrates the Goggles frames used in the experiment.

### 2.2.3. Procedures

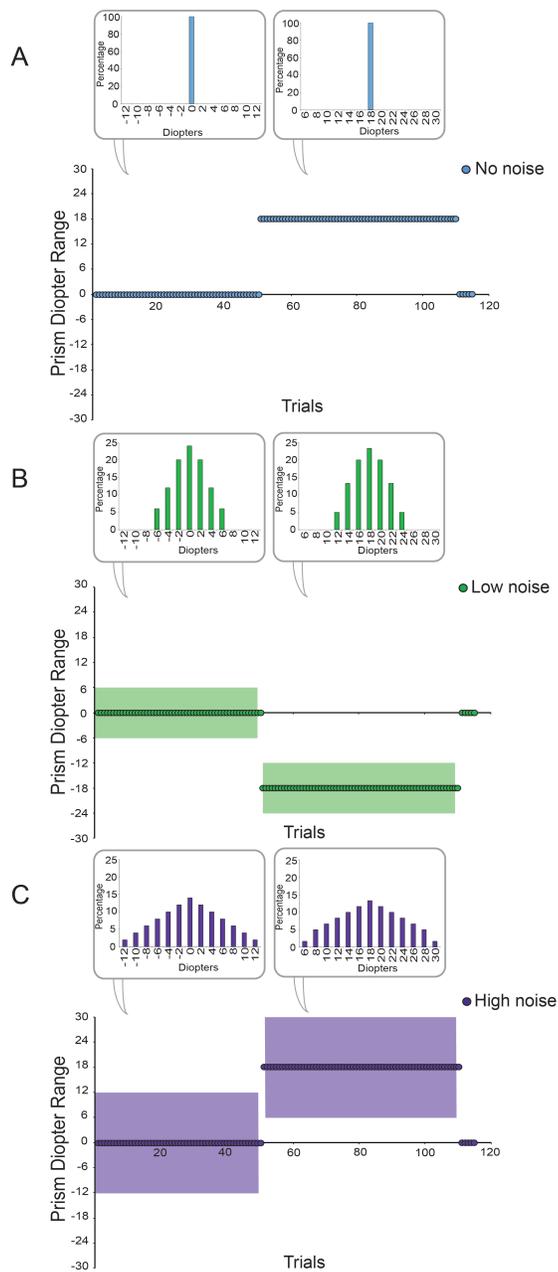
Experimental protocols were composed of 50 baseline, 60 adaptation, and 5 post-adaptation trials. In the baseline and adaptation phases, the prism lenses that subject wore varied in strength and perturbation direction on a trial-by-trial basis. We varied the mean of these shifts to create an adaptation paradigm and the range to create three experimental conditions with distinct levels of uncertainty (referred to as noise): no noise, low noise and high noise. The mean prism shift in these conditions was 0 (0 degrees) or 18 diopters (~10.3 degrees) in the baseline and adaptation phases, respectively. The no noise condition consisted of a constant 0 diopter lens in the baseline phase and a constant 18 diopter lens in the adaptation phase. The low noise condition consisted of lenses with a range of  $\pm 6$  diopters (in 2 diopter increments) around the mean prism shift of the baseline and adaptation phases. The high noise condition consisted of lenses with a range  $\pm 12$  diopters (in 2 diopter increments) around the mean prism shift of the baseline phase and adaptation phases. Importantly, the mean of the distributions of lenses in both noise conditions were similar to the no noise condition in the baseline and adaptation phases. After each adaptation phases, five post-adaptation trials with no visual shifts (i.e., 0 degrees) were also included to assess the magnitude of each adaptation. Figure 3 shows all the lenses used in the experiment.



**Figure 3. Prism lenses used.**

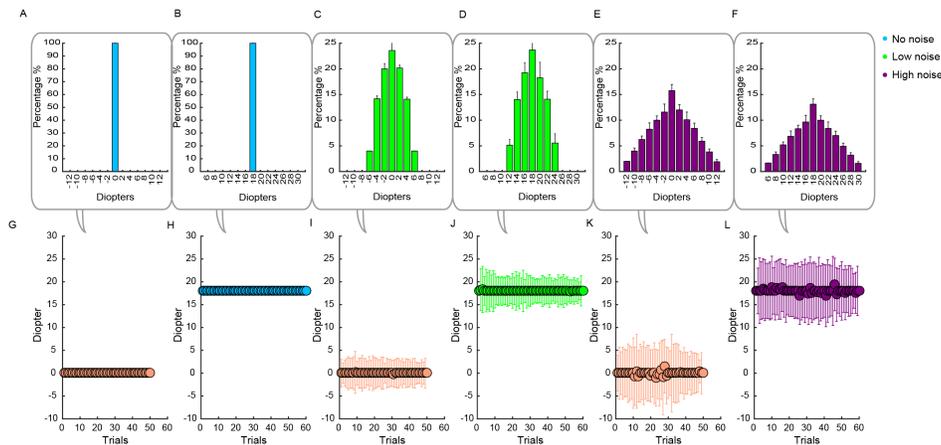
Lenses values are shown in diopters (1 diopter ~ 0.57 degrees).

For each noise condition and phase, the frequency of the specific lenses for a given range was based on a Gaussian distribution. A custom-written MATLAB (Mathworks) program was created to randomly generate the order of lenses based on the Gaussian distribution of each experimental condition, and the total number of trials per baseline and adaptation phases. This program also performed 3 iterations that checked and flipped diopter orders, when similar visual perturbations were randomly placed in sequence. This procedure was an attempt to increase the between-trial diopter differences, and thus increase the mapping uncertainty within a given noise condition. Probe trials with the values of the mean of each respective phase were also placed at the end of the baseline phase, and at the beginning and end of each adaptation phase in all experimental conditions. These trials accounted for different diopter differences in the transition between each phase, and allowed for the same amount of perturbation to occur in the first adaptation trial across all conditions. Higher ranges indicate that more lenses were used and consequently, the frequency of the mean diopter per phase in the protocol dropped from 100% in the no noise to 25% ( $\pm 2.9$ ) and 15% ( $\pm 2.9$ ) in the low and high noise, respectively, thereby increasing uncertainty. A schematic representation of the experimental protocol and distribution of the lenses for each noise condition is shown in Figure 4. Figure 5 shows the actual mean and standard deviation (SD) of the distribution of lenses and protocols across all conditions.



**Figure 4. Schematic of the experimental protocol**

Panels A, B & C illustrate the no, low and high noise protocols. Shading indicates the range of possible prism shifts. The Gaussian distributions show the percentage of each diopter in a given phase of the protocol.



**Figure 5. Actual protocol**

Panels A-F illustrate the mean and SD of the percentage of distribution of lenses. Panels G-L illustrate the mean and SD of all the diopeters used in the experiment. The mean of diopeters in the baseline was kept constant in the no (G) low (I) and high (K) conditions. Likewise, panels H, J and L also show that the mean was constant in the adaptation in the no, low and high conditions, respectively. Error bars indicate the SD of all prism shifts.

All subjects performed all experimental conditions in a fully counterbalanced design that accounted for the order of experimental conditions (see Table 1A and 2) and side of the induced visuomotor perturbation (see Table 1B and 2). This experimental approach was used to minimize the effects of learning across conditions, and to allow for a within-subject design. Due to time constraints and to prevent subject fatigue, two conditions separated by a 10min rest break were performed in one day, and the third condition was performed during a second session with an average interval between testing sessions of  $6.29 \pm 3.09$  days. The duration of the experimental sessions were approximately 2 hours on the first day, and 1 hour on the second day.

A			
Conditions	First block	Second block	Third block
No noise	~ 33%	~ 33%	~ 33%
Low noise	~ 33%	~ 33%	~ 33%
High noise	~ 33%	~ 33%	~ 33%

B			
Adaptation	First block	Second block	Third block
Rightward	50%	50%	50%
Leftward	50%	50%	50%

**Table 1. Counterbalance of conditions (A) and side of visuomotor adaptation (B).**

Day	Block	Trials / Phase	# Order 1		# Order 2		# Order 3	
			Noise	(Shift direction, Range) in diopter	Noise	(Shift direction, Range) in diopter	Noise	(Shift direction, Range) in diopter
Day 1	1	50 Baseline	No	(0, 0)	High	(0, ±12)	No	(0, 0)
		60 Adaptation	No	(18 right, 0)	High	(18 left, ±12)	No	(18 left, 0)
		05 Post-Adaptation	-	(0, 0)	-	(0, 0)	-	(0, 0)
	2	50 Baseline	Low	(0, ±6)	Low	(0, ±6)	High	(0, ±12)
		60 Adaptation	Low	(18 left, ±6)	Low	(18 right, ±6)	High	(18 right, ±12)
		05 Post-Adaptation	-	(0, 0)	-	(0, 0)	-	(0, 0)
Day 2	3	50 Baseline	High	(0, ±12)	No	(0, 0)	Low	(0, ±6)
		60 Adaptation	High	(18 right, ±12)	No	(18 left, 0)	Low	(18 left, ±6)
		05 Post-Adaptation	-	(0, 0)	-	(0, 0)	-	(0, 0)
Day	Block	Trials/Phase	# Order 4		# Order 5		# Order 6	
			Noise	(Shift direction, Range) in diopter	Noise	(Shift direction, Range)	Noise	(Shift direction, Range) in diopter
Day 1	1	50 Baseline	Low	(0, ±6)	Low	(0, ±6)	High	(0, ±12)
		60 Adaptation	Low	(18 left, ±6)	Low	(18 right, ±6)	High	(18 right, ±12)
		05 Post-Adaptation	-	(0, 0)	-	(0, 0)	-	(0, 0)
	2	50 Baseline	High	(0, ±12)	No	(0, 0)	No	(0, 0)
		60 Adaptation	High	(18 right, ±12)	No	(18 left, 0)	No	(18 left, 0)
		05 Post-Adaptation	-	(0, 0)	-	(0, 0)	-	(0, 0)
Day 2	3	50 Baseline	No	(0, 0)	High	(0, ±12)	Low	(0, ±6)
		60 Adaptation	No	(18 left, 0)	High	(18 right, ±12)	Low	(18 right, ±6)
		05 Post-Adaptation	-	(0, 0)	-	(0, 0)	-	(0, 0)
Day	Block	Trials / Phase	# Order 7		# Order 8		# Order 9	
			Noise	(Shift direction, Range) in diopter	Noise	(Shift direction, Range) in diopter	Noise	(Shift direction, Range) in diopter
Day 1	1	50 Baseline	No	(0, 0)	High	(0, ±12)	No	(0, 0)
		60 Adaptation	No	(18 left, 0)	High	(18 right, ±12)	No	(18 right, 0)
		05 Post-Adaptation	-	(0, 0)	-	(0, 0)	-	(0, 0)
	2	50 Baseline	Low	(0, ±6)	Low	(0, ±6)	High	(0, ±12)
		60 Adaptation	Low	(18 right, ±6)	Low	(18 left, ±6)	High	(18 left, ±12)
		05 Post-Adaptation	-	(0, 0)	-	(0, 0)	-	(0, 0)
Day 2	3	50 Baseline	High	(0, ±12)	No	(0, 0)	Low	(0, ±6)
		60 Adaptation	High	(18 left, ±12)	No	(18 right, 0)	Low	(18 right, ±6)
		05 Post-Adaptation	-	(0, 0)	-	(0, 0)	-	(0, 0)
Day	Block	Trials/Phase	# Order 10		# Order 11		# Order 12	
			Noise	(Shift direction, Range) in diopter	Noise	(Shift direction, Range)	Noise	(Shift direction, Range) in diopter
Day 1	1	50 Baseline	Low	(0, ±6)	Low	(0, ±6)	High	(0, ±12)
		60 Adaptation	Low	(18 right, ±6)	Low	(18 left, ±6)	High	(18 left, ±12)
		05 Post-Adaptation	-	(0, 0)	-	(0, 0)	-	(0, 0)
	2	50 Baseline	High	(0, ±12)	No	(0, 0)	No	(0, 0)
		60 Adaptation	High	(18 left, ±12)	No	(18 right, 0)	No	(18 right, 0)
		05 Post-Adaptation	-	(0, 0)	-	(0, 0)	-	(0, 0)
Day 2	3	50 Baseline	No	(0, 0)	High	(0, ±12)	Low	(0, ±6)
		60 Adaptation	No	(18 right, 0)	High	(18 left, ±12)	Low	(18 left, ±6)
		05 Post-Adaptation	-	(0, 0)	-	(0, 0)	-	(0, 0)

**Table 2. Counterbalanced design.**

In the beginning of both testing sessions, participants were provided with specific verbal instructions and an experimenter demonstrated the experimental task. Instructions emphasized that the goal of the task was to step onto the centre of the ML location of the target while walking consistently along the walkway, without stopping, and to look down to see foot contact with respect to the target every trial. Subjects were also instructed to wait for a “go” command to open their eyes and start walking, and to have their eyes open only when performing the task. This was done to avoid any further adaptation in the transition between trials. A laboratory assistant was in charge of guiding the subjects with their eyes closed back to the starting position, and to manually change the lenses on a trial-by-trial basis. Familiarization trials preceded the actual protocols (~ 5 trials) to ensure that all subjects understood the experimental instructions and procedures and were able to perform the task.

To record movement, infrared-emitting diodes (IREDS) were placed on the chest and bilaterally on the mid-feet, approximately at the lateral cuneiforms. Kinematic data were recorded at a sampling frequency of 100 Hz by an Optotrak Certus motion capture camera (Northern Digital Inc., Waterloo, Ontario), positioned perpendicular to the experimental walkway. A Panasonic high-definition camcorder (model HDC-SD60) was also used to record videos of each trial.

#### **2.2.4. Data and Statistical Analysis**

All data were analyzed using custom-written MATLAB 2014b (Mathworks) programs. In this experiment, the main measurement of performance was the ML end-point error of foot placement relative to the center of the target (Figure 2B). This measurement was calculated by analyzing the kinematic data from the IRED marker of the right mid-foot. Gait speed was calculated from the IRED marker from the chest. First, a cubic spline was used to interpolate all the kinematic data that had missing values, and its output was then filtered using a recursive fourth-order low-pass Butterworth filter (cut-off frequency of 6 Hz). Subsequently, first and second derivatives of each marker were calculated to extract the velocity and acceleration profiles, respectively. Foot placement events were defined as the time of stabilization of the antero-posterior velocity and acceleration profiles to zero. This time value was paired with the ML values to calculate

the ML value of foot placement relative to the ML center of the target. Positive error values represent errors to the right of the target, and negative error values represent error to the left of the target (see Figure. 2B).

Subsequent analysis of the ML foot placement errors included the calculation of the time constant of error decay in the adaptation phase. This measure indicates how fast the subjects decreased movement errors while adapting to the mean shift. A single exponential function with an amplitude and time constant parameter was fit to the data through an unconstrained nonlinear optimization in MATLAB (`fminsearch`, `optimset`) that minimized the sum of the squared differences between an exponential model and the data. Exponential fits have been previously used to analyze the time constant of movement error reduction in many visuomotor adaptation studies both in reaching and walking (Morton and Bastian, 2004; Martin et al., 2005; Gidley Larson et al., 2008; Alexander et al., 2011). Measured time constants were then used for identifying the response time at 95% of the total decay (time constant multiplied by 3).

Additionally, residual errors were analyzed to characterize movement errors induced by the diopter noise. In the residual analysis, individual errors in the baseline and adaptation phases were subtracted by the mean baseline error and the exponential fits, respectively. To match these residual errors, all protocols were also subtracted by the mean no noise protocol. This procedure removed the adaptation effect by removing the decay of errors and the mean visuomotor perturbation from the data and protocols, respectively. This procedure allowed us to calculate the residual errors caused by diopters regardless the protocol phase. Variability in the adaptation phase was then computed as a root mean square error (RMSE) and variability in the baseline was calculated as a standard deviation (SD). These measures were used to determine whether the experimental protocols created the expected sensorimotor uncertainty conditions. Thus, the variability of residual errors in the baseline and adaptation phases was compared between all uncertainty conditions.

To further quantify how subjects adapted in the face of uncertainty, we compared the performance at specific trials (i.e., last baseline, first adaptation, last adaptation, first and mean post adaptation trials). These probe trials had lens values of the mean of each

respective phase and thus allowed comparisons across conditions. Statistical analyses were performed using two-way repeated-measures ANOVAs (uncertainty x phases) and Tukey post hoc tests were performed when the ANOVAs yielded significant results.

To determine the effects of sensorimotor uncertainty on visuomotor adaptation during walking we compared the means of the response times of adaptation, and the mean of trials 2 to 9 in the adaptation across all uncertainty conditions. The mean of groups of trials in early adaptation have also been previously used as a measurement of the adaptation rates (Krakauer et al., 2005; Mazzoni and Krakauer, 2006). While the response time captures how long it took for subjects to reduce movement errors in the adaptation phase (~95% of the total decay), the mean of trials instead focuses on the period of early adaptation. We also created regression models to test for a relationship between adaptation rates (response time and mean early adaptation) and individual baseline movement variability. We used one-way repeated-measures ANOVAs in these comparisons and Tukey post hoc tests were performed when the ANOVAs yielded significant results.

Additionally, we created regression models for each individual subject to determine the effects of uncertainty on the relationship between residual movement errors and their respective diopters. The mean slope of residual errors on the current ( $k$ ) and a subsequent trial ( $k+1$ ) by their respective diopters was compared using two-way repeated-measures ANOVAs (uncertainty x trials) and Tukey post hoc tests were performed when the ANOVAs yielded significant results.

All statistical analyses were performed using JMP 10 software (SAS) with a  $\alpha$ -level of 0.05.

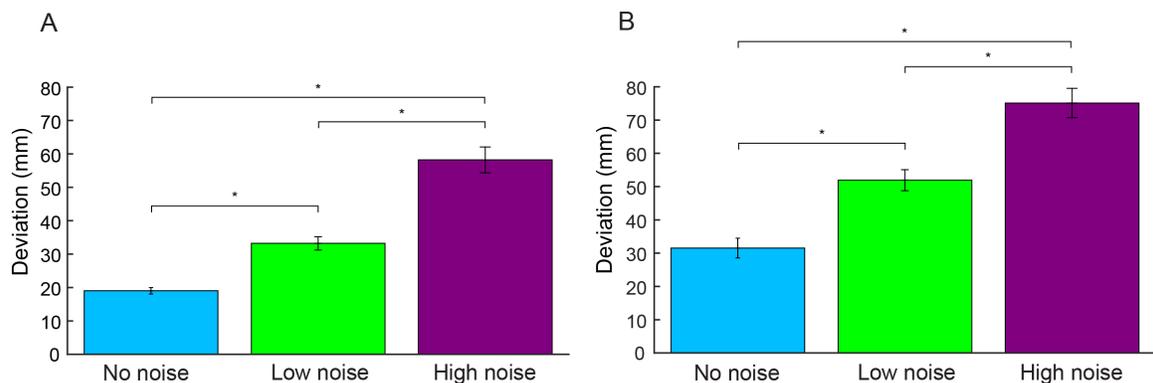
## **2.3. Results**

All subjects complied with the test instructions and were able to perform the walking task consistently throughout the experimental conditions. More importantly, subjects walked at a quick pace throughout the experiment and did not stop in the middle of trials, which diminished any contributions of online corrections. Results

showed no significant main effects of noise conditions ( $F_{2,115} = 1.09$ ,  $p > 0.33$ ), phases ( $F_{1,115} = 0.83$ ,  $p > 0.36$ ) or interactions ( $F_{2,115} = 0.73$ ,  $p > 0.48$ ) on walking speed, which averaged  $1.9 \pm 0.3$  m/s across all trials.

### 2.3.1. Movement Error Variability

Our results first show that movement variability in the baseline and adaptation phases increased when increasing sensorimotor uncertainty (Figure 6). This result is supported by our ANOVA main effect of condition ( $F_{2,115} = 122.44$ ,  $p < 0.001$ ) and phase ( $F_{1,115} = 54.64$ ,  $p < 0.001$ ). We found no significant interaction effect ( $F_{2,115} = 0.71$ ,  $p = 0.48$ ), indicating that the effect of variability is independent of the phase of the protocol. Tukey post-hoc tests showed differences across all noise conditions. The variability in the low and high noise conditions were found to be 74.6% and 206.0% greater than the no noise condition in the baseline, and 64.7% and 138.2% greater than the no noise in the adaptation, respectively. This finding suggests that our experimental conditions created increasing levels of sensorimotor uncertainty, which affected the performance by increasing the levels end-point error variability.



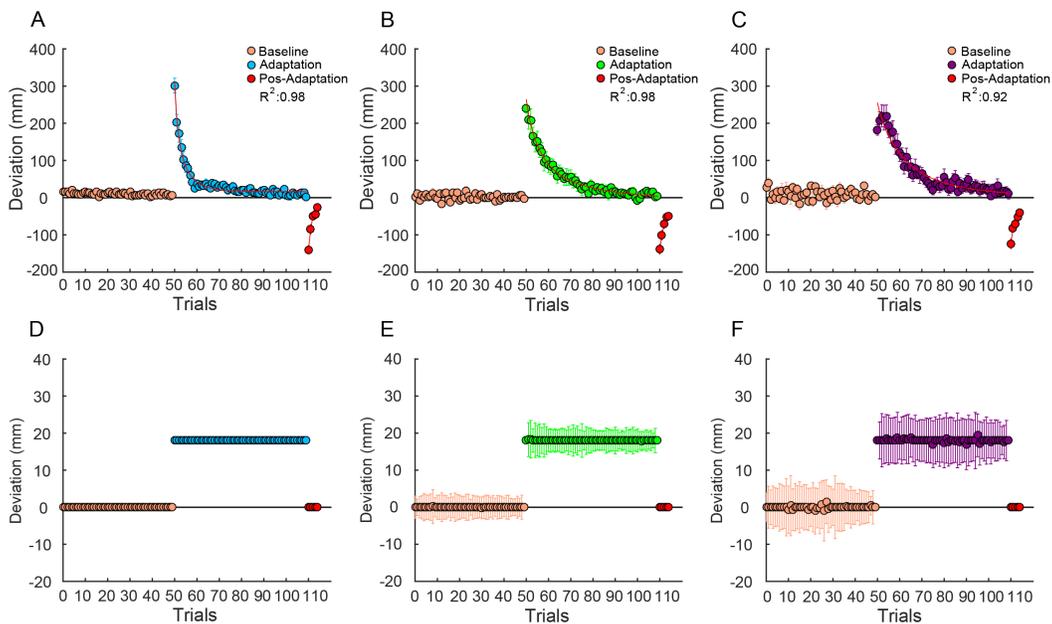
**Figure 6. Lateral end-point error variability**

A) Group mean baseline standard deviation (SE) for each uncertainty condition. B) Group mean residual RMSE (SE) of the adaptation for each condition. These results show that the protocol created uncertainty, and increased movement variability in the baseline and adaptation phases of the protocol. \*Significant differences are shown based on Tukey's post hoc tests ( $P < 0.05$ ).

### 2.3.2. Visuomotor Adaptation

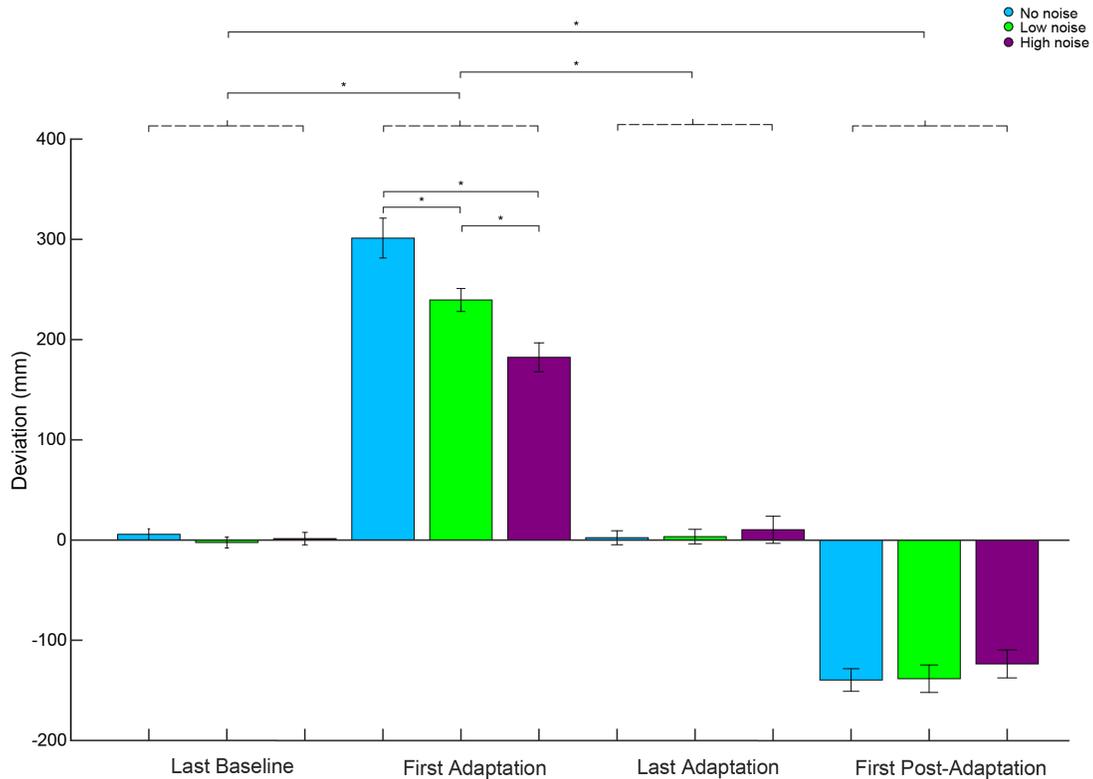
Results of the analysis of the probe trials (i.e., last baseline trial, the first and last adaptation phase trial, and the first post-adaptation trial) showed that all subjects adapted in all noise conditions. In particular, in the initial exposure to the prisms, there was a large deviation in foot placement with respect to the target, which subjects were able to adapt and return to baseline standards by the end of the adaptation phase. Upon the removal of the prisms, there were also significantly large negative aftereffects in all noise conditions (see Figure. 7 A-C profiles).

The large error in the first adaptation trial is shown by our main phase effect of the probe trials, ( $F_{3,251} = 508.12$ ,  $p < 0.001$ ). In particular, Tukey post-hoc tests showed differences in the comparison of the last baseline and first prism-adaptation trial ( $P < 0.001$ ). Over repeated trials, our results also showed a reduction of these errors (first vs. last prism-adaptation trials,  $P < 0.001$ ), which is an indication that performance returned to near-baseline levels (baseline vs. late-adaptation phase,  $P > 0.05$ ). After subjects removed the prisms in the post-adaptation phase there was also a significant negative aftereffect ( $P < 0.001$ ). Evidence of aftereffects is also another indication that subjects adapted in all noise conditions (Shadmehr, 2004). Figure 8 shows the mean probe trials with these respective effects.



**Figure 7. Mean lateral end-point errors and mean protocol by trials.**

Mean (SE) movement errors over trials in the no noise (A), low noise (B) and high noise (C) conditions. The bottom row shows the mean (SD) protocol in its respective condition (D No noise, E low noise and F high noise).



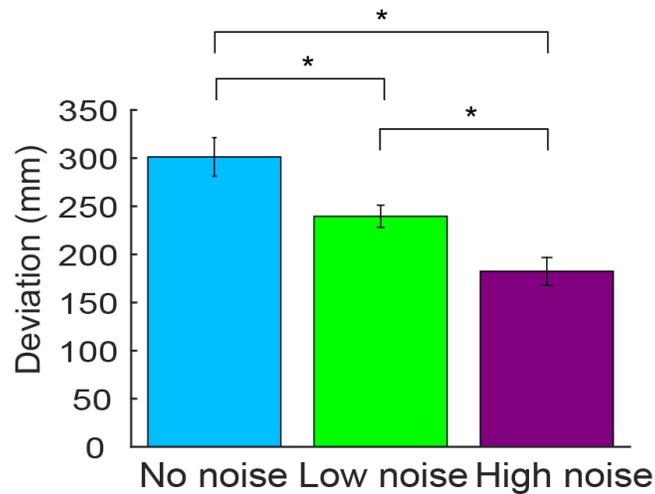
**Figure 8. Mean lateral end-point errors during probe trials**

Mean Probe trials for each uncertainty condition. These results showed that subjects adapted, returned performance to baseline levels, and showed large aftereffects from the prism adaptation in all noise conditions. \* indicates the significant main effects ( $P < 0.05$ ).

### 2.3.3. Uncertainty in Visuomotor Adaptation

The main findings emerging from this study was that uncertainty modulated the initial responses in the adaptation phase, the adaptation rate, and the trials early in the adaptation. First, our results show that the mean first adaptation trial decreased as a function of uncertainty. This was supported by a main effect of noise condition on errors

during the first adaptation trial ( $F_{2,45} = 13.90$ ,  $p < 0.001$ ), in which Turkey post-hoc tests indicated differences in the first adaptation trial across all noise conditions. The first adaptation trial in the low and no noise conditions were found to be 31.4% and 65.2% greater than the high noise condition. This effect is shown in Figure 9.



**Figure 9. Mean first adaptation trials**

Mean first adaptation trial for each uncertainty condition. This result show that the initial responses to visuomotor perturbations happened as a function of sensorimotor uncertainty.\* indicates the significant main effects ( $P < 0.05$ ).

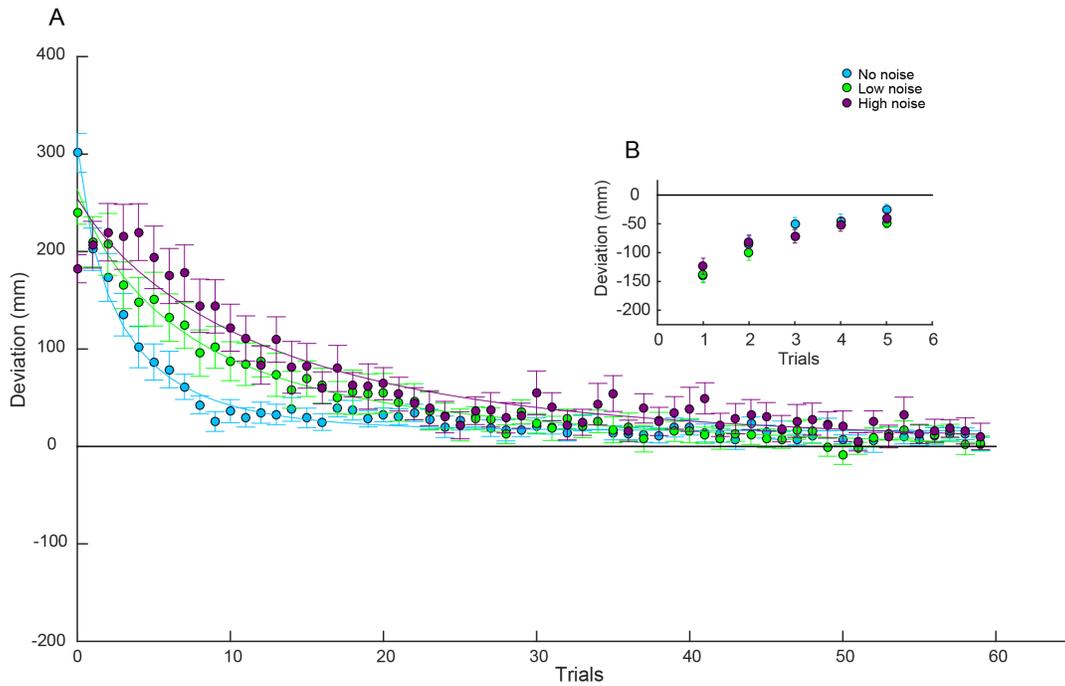
Additionally, our results showed that adaptation rates were slower when increasing sensorimotor uncertainty. In this experiment, we used two measurements to track the adaptation over time. This included the mean response time (3x exponential time constant), and the mean of trials 2 to 9 in early adaptation. The mean response time showed a significant effect of noise condition ( $F_{2,43} = 4.25$ ,  $p < 0.020$ ), and Tukey post-hoc tests identified a significant difference between the no and high noise conditions. Although the mean low noise fell in between the mean of the two other conditions, no further significant differences were found. The mean response time in the low and high noise conditions were 262.5% and 383.2% greater than the no noise condition. The exponential fits in this experiment achieved a  $R^2$  of 0.98 in the no noise, 0.98 in the low noise and 0.92 in the high noise, which indicate that this measurement was a good representation of the adaptation process. On an individual subject basis, the

$R^2$  of the exponential fits ranged from 0.29 to 0.92 in the no noise, 0.24 to 0.78 in the low noise and 0.13 to 0.66 in the high noise condition (see Table 3). The adaptation curves with its respective exponential fits are shown in Figure 10A and 11A. Figure 11B shows a bar plot of the mean response time for each condition.

Similar results were also found in the comparisons of the mean of trials in early adaptation (trial 2 to trial 9). Results of the ANOVA also showed a significant main effect of group, ( $F_{2,46} = 6.18$ ,  $p < 0.004$ ) and subsequent post-hoc tests showed a higher mean in the high noise condition than the mean no noise condition. Also, no significant differences were found in the comparisons with the mean low noise. The mean of trials early in the adaptation in the low and high noise conditions was 42.5% and 75.7% greater than the no noise condition. Figure 11C shows a bar plot of the mean early adaptation for each condition. In conjunction, these findings indicate that sensorimotor uncertainty played a role in the adaptation process.

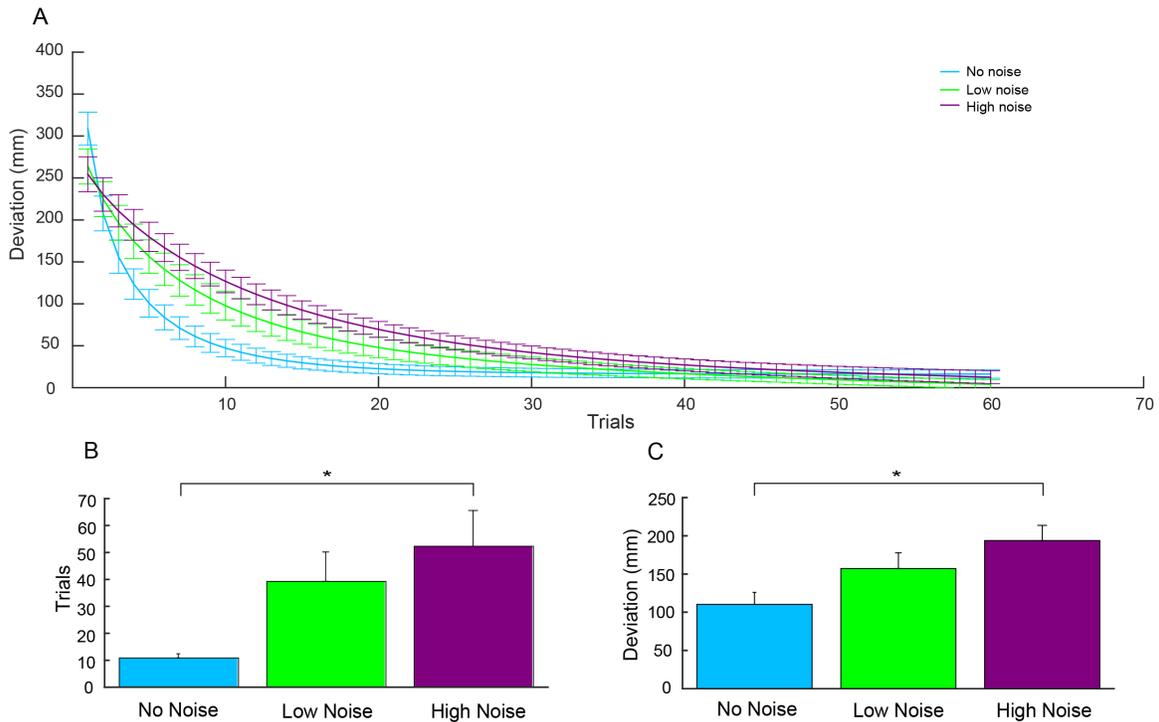
Subject	No Noise	Low Noise	High Noise
1	0.7329	0.4198	0.131
2	0.7227	0.3162	0.3282
3	0.5621	0.5738	0.2715
4	0.8117	0.5827	0.4353
5	0.9151	0.7345	0.2747
6	0.829	0.6476	0.2811
7	0.7269	0.6047	0.28
8	0.5762	0.5387	0.4294
9	0.5206	0.5839	0.4042
10	0.7785	0.7312	0.4989
11	0.4447	0.7787	0.4628
12	0.9107	0.6268	0.6146
13	0.777	0.7195	0.66
14	0.8584	0.5837	0.3853
15	0.8332	0.6957	0.5019
16	0.8638	0.3924	0.5589
17	0.292	0.5061	0.5959
18	0.873	0.6959	0.6474
19	0.4722	0.5395	0.2222
20	0.8035	N/A	N/A
21	0.6517	0.3037	0.5844
22	0.6977	0.4145	0.1975
23	0.6769	0.3567	N/A
24	0.8175	0.2414	0.4834

**Table 3. Individual exponential fits ( $R^2$ ).**



**Figure 10. Mean adaptation (A) and post-adaptation (B) phases by trials**

Mean movement errors over trials (SE) in in the adaptation (A) and post-adaptation phase (B).

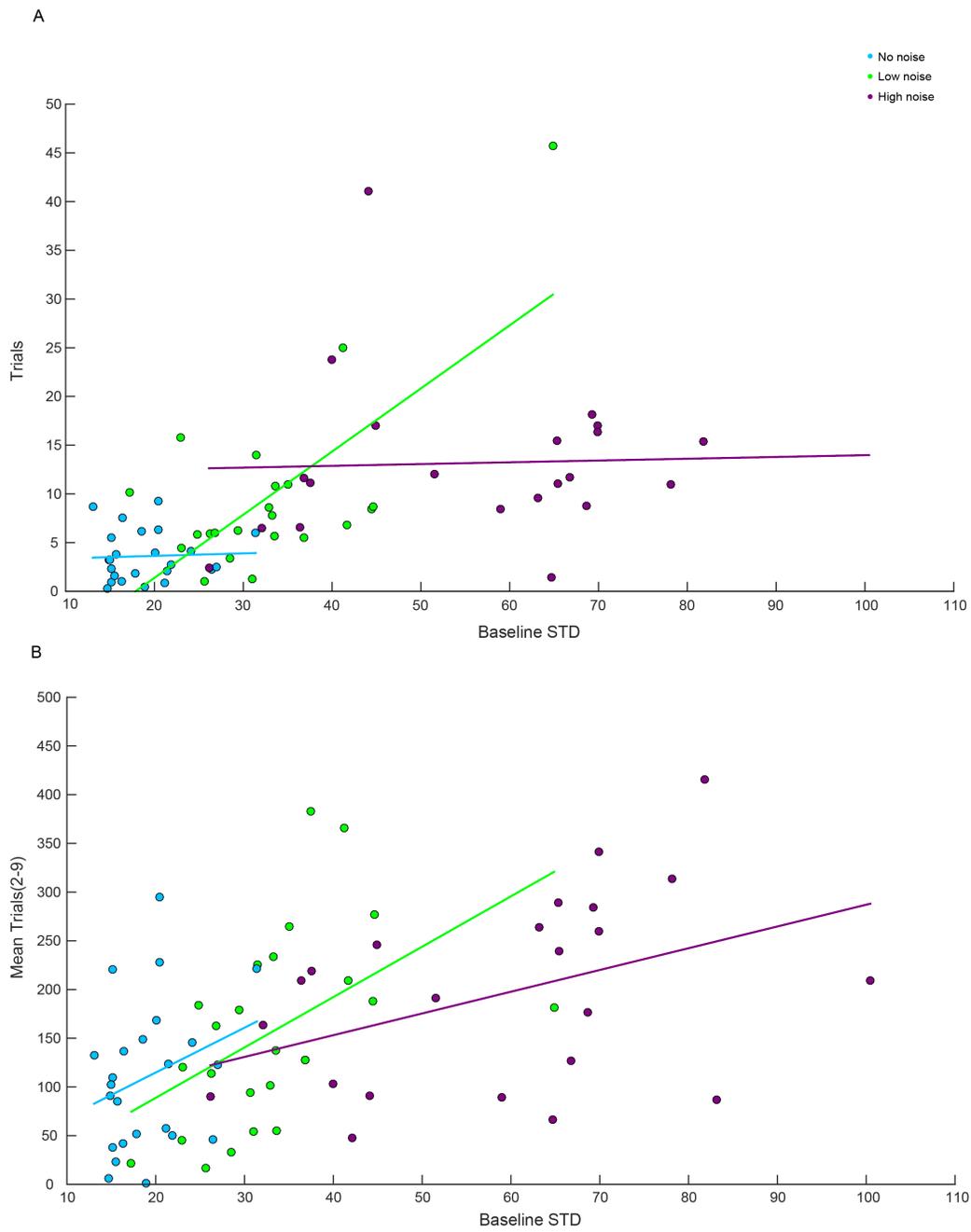


**Figure 11. Mean exponential fits (SE)**

(A). Mean exponential fits (SE), mean response time (B), and mean early adaptation (C) measured the performance in the adaptation of each condition.

To further investigate the effects of sensorimotor uncertainty in the visuomotor adaptation, we also assessed whether baseline variability predicted performance in the adaptation phase. The idea was that movement variability might be a predictor of adaptation rate. We first fit a regression between the exponential response times and the baseline variability in SD. Results showed evidence of significant slope only for the low noise condition ( $F_{1,22} = 17.79$ ,  $p < 0.0004$ ), as such the no ( $F_{1,20} = 0.04$ ,  $p > 0.83$ ), and the high noise slopes ( $F_{1,19} = 0.02$ ,  $p > 0.87$ ) failed to show any significance of a relationship. This evidence was further demonstrated with an interaction effect ( $F_{2,61} = 7.45$ ,  $p < 0.0013$ ), indicating a significant difference between the slopes, in particular in the low noise condition. These regression fits achieved a  $R^2$  of 0.002 in the no noise, 0.47 in the low, and 0.001 in the high noise. Figure 12 (A) shows the outcome of this analysis.

Additionally, we created a regression model between the mean of trials early in the adaptation and baseline variability in SD. Results showed evidence of a significant relationship in the slopes for the Low ( $F_{1,22} = 7.18$ ,  $p < 0.013$ ), and high ( $F_{1,22} = 5.08$ ,  $p < 0.034$ ) noise conditions but no further significance was found for the no noise condition ( $F_{1,22} = 1.84$ ,  $p > 0.18$ ). Also, these regressions yielded no group interaction effects ( $F_{2,66} = 1.11$ ,  $p > 0.33$ ), which indicate no differences between the slopes across noise conditions. This analysis showed a  $R^2$  of 0.07 for the no, 0.24 for the low and 0.18 for the high noise conditions (Figure 12 B). The differences between these measurements of adaptation rate (response time and mean early adaptation) and their distinct variances across subjects might be the reasons for these differences in the results (see error bars in figure 11 B and C). However, overall these results indicate that baseline variability in the face of uncertainty was not a strong predictor of the adaptation rate.

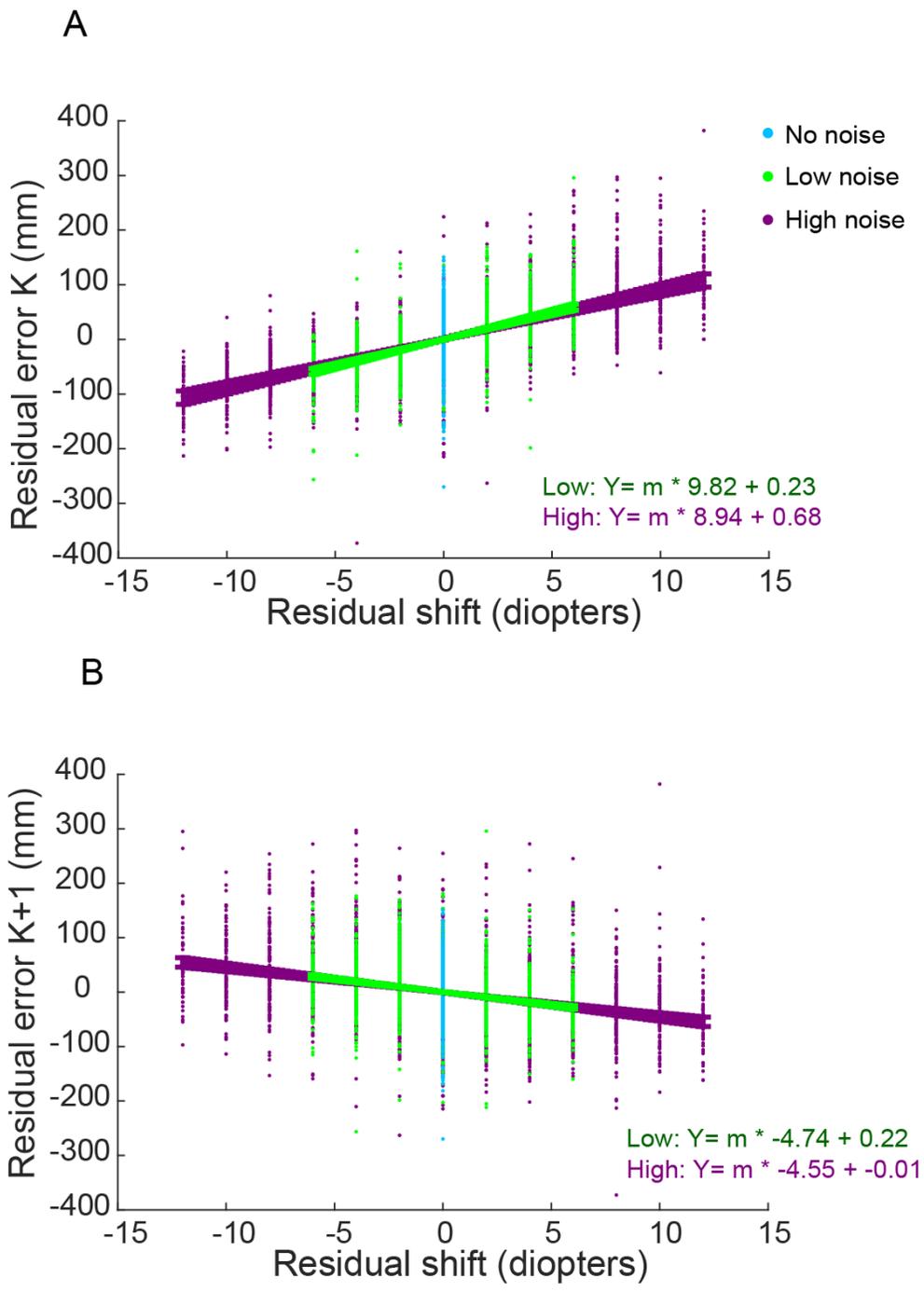


**Figure 12. Relationship between baseline variability and adaptation rates (A) response time and (B) mean early adaptation.**

### 2.3.4. Relationship Between Errors and Diopter Sizes

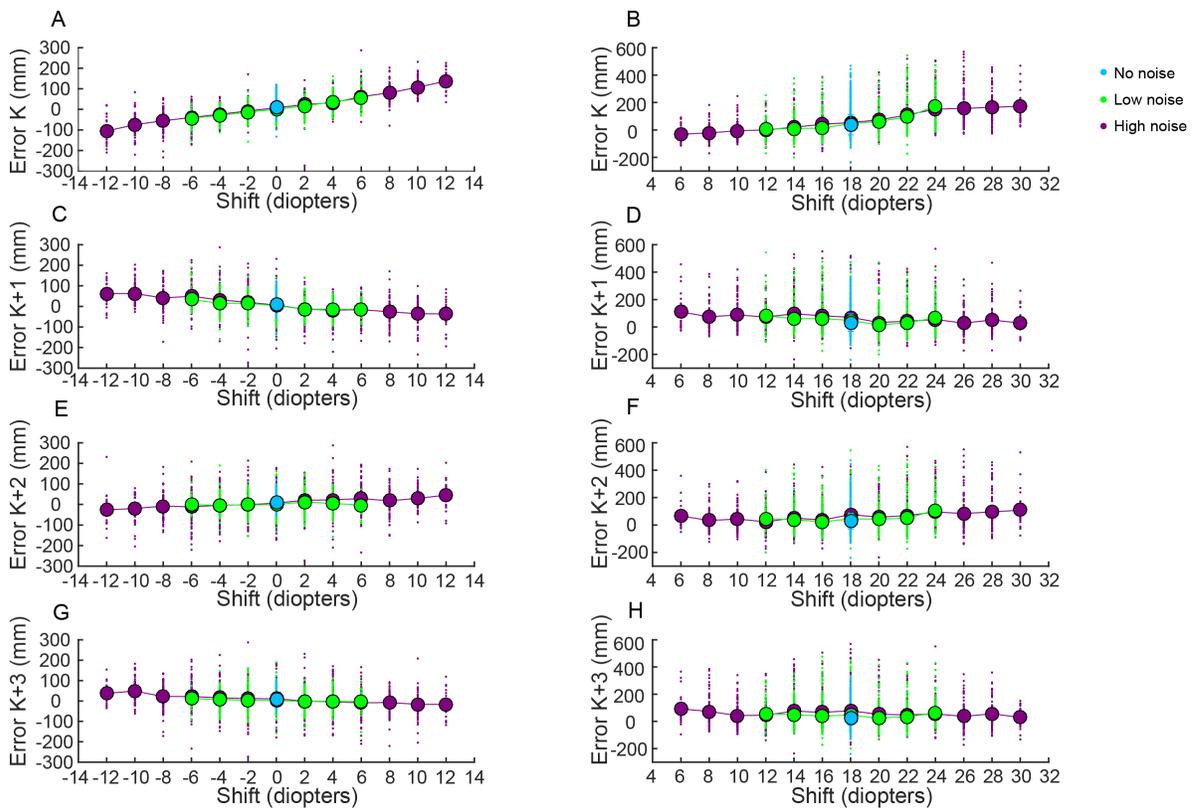
We also investigated the effects of sensorimotor uncertainty in the relationship between movement errors and their respective diopters. The idea was that movements would be less sensitive to diopter magnitude in the high noise condition as a reflection of a shift of reliance of error feedback (Wei and Körding, 2009; 2010). We proceeded by fitting a linear regression between the residual diopters and the residual movement errors for each subject. While we show evidence of a relationship in all noise conditions ( $F_{2,115} = 510.8$ ,  $p < 0.001$ ), there were no differences in the mean slopes of the regressions between low and high conditions ( $F_{1,115} = 0.39$ ,  $p < 0.52$ ). These regression fits resulted in a  $R^2$  of 0.43 in the low and 0.51 in the high noise condition. Figure 13 (A) shows the mean and standard errors of the slopes of this relationship.

In addition, we also asked whether this effect of uncertainty would appear when observing movement errors in a subsequent trial. That is, if a particular visuomotor perturbation would cause changes in subsequent movements over subsequent trials. Thus, we also used linear regressions to compare the relationship between the residual diopters and the residual movement errors in the subsequent trial (see mean slopes in Figure 13B). Results show evidence of a negative relationship in all noise conditions ( $F_{2,115} = 510.8$ ,  $p < 0.001$ ), but still no differences were found in the comparisons between low and high conditions ( $F_{1,115} = 0.39$ ,  $p < 0.52$ ). These regression fits resulted in a  $R^2$  of 0.1 in the low and 0.13 in the high noise condition. Figure 13 (B) shows the mean and standard errors of the slopes of this relationship. Although we did not find any significant main effects of uncertainty in the slopes, this negative relationship shows an influence of a perturbation on a subsequent trial. This carry over can also be observed when plotting the relationship between diopters and the mean movement errors over several subsequent trials (Figure 14).



**Figure 13. Mean regression between residual diopters and errors.**

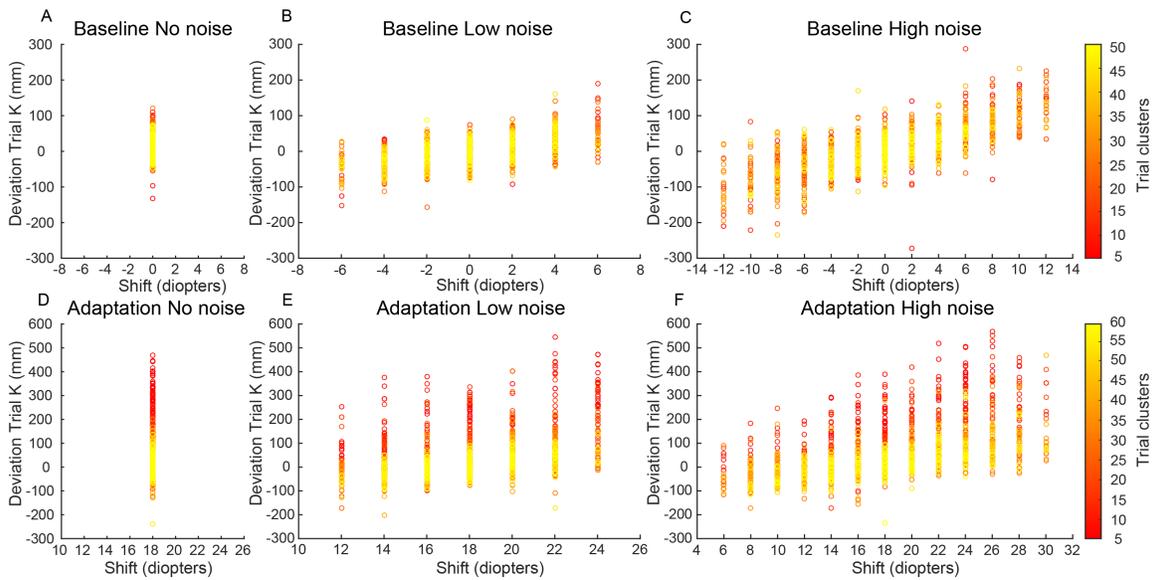
Relationship between the residual diopters and residual movement errors in the current (A) and a subsequent trial (B). Residual analysis removed the adaptation component by subtracting the exponential fits from the errors and the mean diopter in the adaptation from the adaptation protocol.



**Figure 14. Relationship between diopters and movement errors over multiple trials**

Relationship between the movement errors and diopters in the current (A) and subsequent trials (C-H). Panels A, C, E and G refer to the errors in the baseline and B, D, F and H refer to the errors in the adaptation phase.

Subsequently, we further assessed the nature of these relationships by looking at the effects of the order of trials in which a particular diopter was presented to our participants. Figure 15 shows the movement errors by diopter as a density of trial orders. Diopters that appeared early in the protocol (within the first cluster of 5 trials) show higher density of colors in the figure as compared to diopters that appear in the last 5 trials. This analysis shows the trace of adaptation over time. Indeed, results of an ANOVA showed a significant main effect of trial orders between the first and the last cluster in the adaptation of the low noise ( $F_{1,24} = 20.94, p < 0.001$ ), and high noise, ( $F_{1,43} = 12.39, p < 0.001$ ). Thus, this bias of trial order on movement errors may have masked our expected findings in the slopes in Figure 13 across the two noise conditions.



**Figure 15. Density of movement error by diopeters**

Relationship between errors and diopeters. Errors were grouped in clusters that represented their trial orders in each protocol. Errors that A shows no noise baseline, D no noise adaptation, B low noise baseline, E low noise adaptation, C high noise baseline and F high noise adaptation. Errors of a diopter with a higher saturation appeared early in a protocol and errors with lower saturation appeared later in a protocol.

## 2.4. Discussion

When motor commands yield unexpected outcomes, errors are observed, and the nervous system is propelled to change its subsequent commands to improve accuracy. However, movement errors can result from different causes, and be considered either as random or consistent perturbations (Burge et al., 2008). Should the nervous system adapt, it has to decide upon a strategy to improve accuracy by reducing those errors, regardless of the underlying causes. A number of studies in reaching movements have built the idea that the brain employs a predictive mechanism to this problem in a way that it compensates for limitations of sensory feedback and also determines its adaptation strategy (Korenberg and Ghahramani, 2002; Smith et al., 2006; Burge et al., 2008; Wei and Körding, 2010; Marko et al., 2012; Wilke et al., 2013; Castro et al., 2014; Herzfeld et al., 2014). When adapting reaching movements, these experiments revealed that the nervous system approaches errors intelligently by considering the past history of errors to avoid changing movements when it is not necessary for the overall performance. Our results expand these views and suggest that the nervous system also relies on a predictive mechanism, based on reliability of error feedback and prior experiences, when controlling a distinct type of behaviour, that is, visually guided walking.

We tested how subjects adapted to a precision walking task in the face of random and constant perturbations with prism glasses. We made three main observations. First, the magnitude of the first perturbation in the adaptation phase was a function of sensorimotor uncertainty. Second, subsequent adaptation to visuomotor perturbations was also modulated by uncertainty. Third, we found that visuomotor perturbations also bias movements over subsequent trials. Thus, these results provide evidence that adaptation during visually guided walking follows a similar framework to reaching movements.

The fact that the first adaptation trial and the rate of adaptation were modulated by uncertainty suggests that subjects reduced their reliance on feedback and weighted prior experiences more heavily. Research in reaching has shown that this shift occurs given that noise (Faisal et al., 2008) and feedback uncertainty modulate how the

nervous system detects and approaches movement errors (Burge et al., 2008; Wei and Körding, 2010). Since feedback uncertainty causes random errors that would drive movements to worse performance, an optimal strategy requires the brain to consider previous trials to make the nervous system less sensitive to these random errors (Korenberg and Ghahramani, 2002; Burge et al., 2008; Wei and Körding, 2010). As a result, the brain does not rely strictly on feedback, and recognizes that, on average, performance still remains accurate (Korenberg and Ghahramani, 2002; Körding and Wolpert, 2004; 2006; Turnham et al., 2011; Vilares and Körding, 2011). More importantly, reaching studies show that the less importance subjects place on feedback, the more they value their prior experiences from previous trials, which can change how they approach subsequent movements. We observed performance in the low and high noise conditions biased towards prior experiences, which modulated the perception of perturbations in the first and subsequent adaptation trials. Conversely, in the no noise condition, subjects were consistent and relied on the actual feedback about the location of the target and the body to the same degree. This increase in feedback confidence led to large movement errors early in the adaptation and faster detection that a recalibration was required, leading to faster adaptation rates. Research has shown that subjects combine multiple sources of sensory information with prior experience to control and adapt a number of human behaviours, such as force estimation (Körding et al., 2004), reaching (Körding and Wolpert, 2004; Burge et al., 2008; Brouwer and Knill, 2009), pointing (Tassinari et al., 2006), movement timing (Miyazaki et al., 2005), interceptive actions (Kwon and Knill, 2013; Narain et al., 2013), eye movements (Najemnik and Geisler, 2005), and standing balance (Stevenson et al., 2009). Our evidence here suggests that this is also the case during walking.

In our experiment, we observed a slight increase in lateral end-point errors following the first adaptation trial in the high noise condition, which is also a reflection of the sensitivity of the nervous system to errors. The high noise was the condition that led to the highest amount of movement variability, which we suggest led to a greater reduction in the reliance of error feedback. The less the nervous system trusts the error feedback, the longer it takes to use it to define the required amount of correction. Early in the adaptation in the high noise, the nervous system was slow at detecting that a different perturbation was occurring in addition to the noise perturbations. The increase

in errors seems to be a further reflection of this process, showing that sensitivity was strong, and affected goal achievements.

The method of manipulating uncertainty in this experiment should also be emphasized. Previous studies created feedback uncertainty and either blurred or decreased the quality of feedback of the location of the limb in space with respect to a target (Körding and Wolpert, 2004; Burge et al., 2008; Izawa and Shadmehr, 2008; Wei and Körding, 2010; Marko et al., 2012). In our experiment, however, the quality of visual feedback was not reduced. Rather, visuomotor mappings were disrupted, which caused unexpected lateral end-point errors. These manipulations are similar in a sense that both create uncertainty about the cause of the errors and challenge the nervous system when adapting. Thus, in our experiment we show that visuomotor mapping uncertainty modulates errors, which in turn dictates how people adapt. Burge et al. (2008) further studied the nature of random visuomotor mapping uncertainty in visuomotor adaptation but failed to find any effects of uncertainty. However, the task differences or the nature of their perturbations may have caused these differences. For instance, they used a ballistic pointing task and their adaptation protocol was created based on a random walk of perturbations, which forced subjects to adapt to an ever-changing perturbation rather than a constant mean.

In addition to these findings, we expected a non-linear relationship between residual errors and diopters magnitude to be more evident in the high noise condition. Specifically, this would lead to smaller slopes in the high noise condition indicating that subjects are less affected by high perturbation magnitudes due to the shift of reliance of error feedback observed in our other measurements (Wei and Körding, 2009; 2010). While our results show no differences between uncertainty conditions, it also revealed that the nature of our protocol restricted this type of analysis (see Figure 15). Our adaptation to a change in the mean of visuomotor perturbations allowed learning to accumulate, as subjects adapted and reduced the errors over time. In fact, previous studies investigating the relationship between visuomotor perturbations and movement errors have instead focused on trial-by-trial adaptation instead of a change in the mean of perturbations (Wei and Körding, 2009; 2010). Despite these results, we observed a positive relationship between perturbation magnitude and movement errors on the same

trial, a relationship that also affected movements on subsequent trials. In particular, when looking at the relationship between perturbation magnitude and movement errors on a subsequent trial we found evidence of a negative relationship, indicating that subjects showed a tendency of changing subsequent movements based on a previous perturbation. Similar relationships between visuomotor perturbations and movement errors have been reported in the adaptation of reaching movements (Wei and Körding, 2010). These findings cannot be explained only by the use of feedback, because we still find that movements are affected by diopters from previous trials. Thus, this is additional evidence that nervous combines feedback with previous experiences when planning subsequent walking movements in a way similar to reaching. Overall, our findings suggest that the nervous system uses an internal model for the control of visually guided walking, which is sensitive to error feedback when adapting to visuomotor perturbations.

In this thesis, we present a different view for the neural control of walking. As opposed to simply feedback control, we approach it from the perspective of motor predictions and state estimation, similar to the control of reaching movements. We showed that the nervous system integrates expectancy with feedback, weighted by its reliability, when controlling visually guided walking. As such, these results support the hypothesis that similar mechanisms might be used in the planning stages of both reaching and walking movements (Georgopoulos and Grillner, 1989; Dietz, 2002). Indeed, a wealth of studies has emphasized the neural overlaps in the control and adaptation across these two tasks. A healthy cerebellum is critical in the adaptation to visuomotor perturbations during reaching and walking (Morton and Bastian, 2004; Donchin et al., 2012). The PPC is largely active during the error reduction process during visuomotor adaptation in reaching (Clower et al., 1996; Inoue et al., 2000; Culham et al., 2006; Girgenrath et al., 2008; Chapman et al., 2010; Tan et al., 2014), and this area has been also shown to play a major role in planning visually guided gait modifications (Lajoie and Drew, 2007; Drew et al., 2008a; Lajoie et al., 2010; Drew and Marigold, 2015). Together, these areas might be involved in dealing with error feedback sensitivity while comparing predicted with actual outcomes of both hand and foot movements. Our current results provide the requisite behavioral links for further investigations of such neural suggestions.

## **Chapter 3. General Discussion**

### **3.1. Neural Mechanisms**

The neural mechanisms of visuomotor adaptation during walking are still largely unknown as compared to reaching. Given the similarities in behavioural findings between our results and those found in the reaching literature, it is likely that common areas are involved in error detection and subsequent adaptation during walking.

The cerebellum has long been demonstrated to play a role in motor adaptation (Wolpert et al., 1998b; Kawato, 1999; Mauk et al., 2000; Cerminara et al., 2009; Norris et al., 2011; Donchin et al., 2012; Schlerf et al., 2012; Gibo et al., 2013; Nguyen-Vu et al., 2013; Guo et al., 2014). It is thought to receive an efference copy of a motor command from the primary motor cortex, which allows it to make predictions with regard to the sensory consequences of motor commands (Wolpert and Kawato, 1998; Wolpert et al., 1998b; Shadmehr et al., 2010). In addition, research has shown that the cerebellum is involved in the process of error corrections. It was originally thought that cerebellar complex spikes (low frequency) generated by climbing fiber connections to Purkinje cells represent an error signal (Kitazawa et al., 1998). Subsequent research, however, demonstrated that the probability of these spikes are also modulated by errors of different sizes (Soetedjo and Fuchs, 2006). More recently, research suggests that complex spikes may in fact encode error sensitivity (Marko et al., 2012). Purkinje cells also show simple spikes, which occur at a higher frequency given inputs from parallel fibers (Miall et al., 1998). These spikes also convey error signals (Popa et al., 2013). Purkinje cells in this case are important, as they guide signals that leave the cerebellar cortex to different brainstem and cortical regions, contributing to movement corrections. Not surprisingly, research with cerebellar patients has indicated that a healthy

cerebellum is critical in the adaptation to visuomotor perturbations during reaching and walking (Morton and Bastian, 2004; Donchin et al., 2012). For reaching, this is also supported by imaging studies examining prism adaptation (Luauté et al., 2009; Chapman et al., 2010). Thus, we can speculate based on our results that a cerebellar mechanism is an important structure when considering movement errors in a visually guided walking task.

Further research using imaging techniques has also identified that the PPC is largely active during the error reduction process of visuomotor adaptation (Clower et al., 1996; Inoue et al., 2000; Culham et al., 2006; Girgenrath et al., 2008; Luauté et al., 2009; Chapman et al., 2010). More recently, Tan et al. (2014) recorded EEG waves while subjects used a joystick to move a cursor to a target. When different visuomotor perturbations were applied, they observed decreased  $\beta$  event-related synchronization, especially in the PPC, according to the saliency of errors. Thus, they suggested that this region was involved in the neural mechanisms that evaluate errors. These results are not surprising considering that the PPC receives multiple sources of feedback, including vision and proprioception, and plays a strong role in movement planning related to reaching (Kalaska et al., 1983; Snyder et al., 1997; Batista et al., 1999; Desmurget et al., 1999; Pisella et al., 2000; Buneo et al., 2002; Della-Maggiore et al., 2004; Van Der Werf et al., 2010; Vesia et al., 2010; Vesia and Crawford, 2012) as well as visually guided gait modifications (Lajoie and Drew, 2007; Drew et al., 2008a; Lajoie et al., 2010). Together, these findings suggests a parieto-cerebellar network likely deals with ambiguous movement errors (Chapman et al., 2010). Indeed, Luauté and colleagues (2009) proposed that parietal areas are involved in error detection and the cerebellum in further spatial realignment. In this study, we propose that the PPC also plays a role in planning visually guided walking and it does so by evaluating errors accordingly to their relevance. Its output is then transferred to other cortical and subcortical regions, such as the cerebellum, pre-motor and primary motor cortex, which then drives movement corrections.

Adaptation ultimately requires a complex integration of cortical, subcortical, and spinal input. For instance, spinal pathways project important sensory feedback to supraspinal centres necessary for adaptive behaviour. The spinocerebellar system

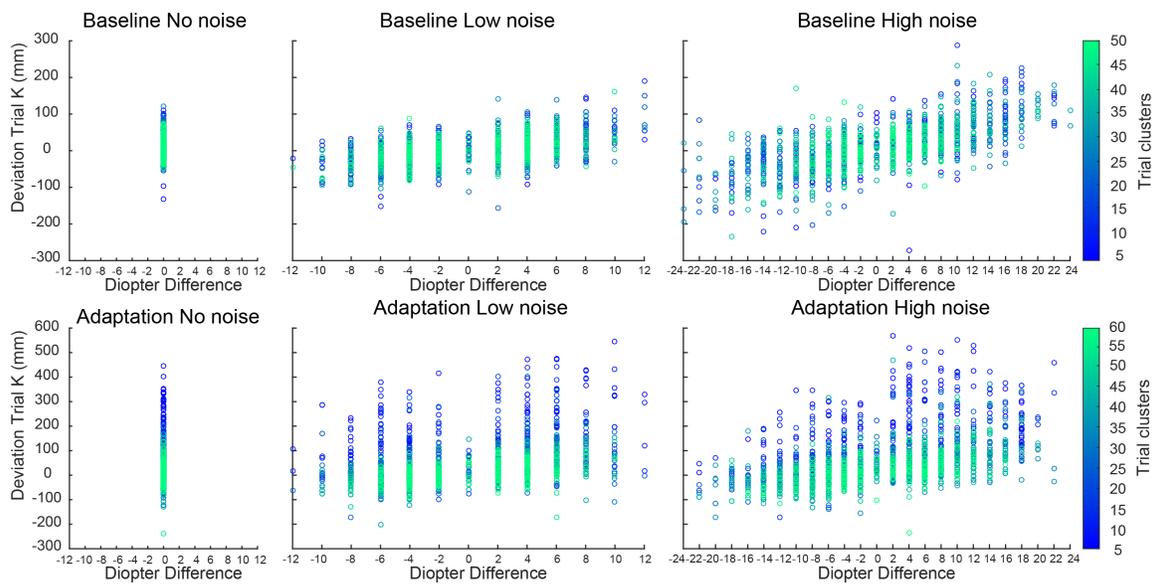
projects this information to the cerebellum. Networks within the dorsal portion of this tract are known to provide the cerebellum with specific proprioception feedback about state of the hind limbs (Lundberg and Weight, 1971; Bosco and Poppele, 2001; Bosco et al., 2006). In contrast, neurons in the ventral portion are known to be active by networks in the CPG, thus providing the cerebellum with information about the state of the spinal rhythms (Kandel, 2013). The cerebellum can then act as a comparator between the actual movements of the legs from limb feedback (dorsal spinocerebellar tract) and the intended movements from the CPGs (ventral spinocerebellar tract). The result of this comparison enables the cerebellum to inform a corrective signal to subsequent subcortical and cortical structures. This process is thought to lead to adjustments in the locomotor pattern when gait movements are unexpectedly deviated. In addition, supraspinal regions, including cortical and subcortical, work together and yield descending commands that are combined into the circuits of the spinal cord, providing further information for movement control. In particular, it is thought that supraspinal descending commands are superimposed onto CPG activity within the spinal cord, allowing for flexible changes in gait based on vision and further sensory information (Drew, 1991; Taga, 1995; Krouchev and Drew, 2013).

In this experiment, we also speculate that a complex integration of cortical, subcortical, and spinal regions are critical for visuomotor adaptation during walking. Cerebellum and the PPC are important for error detection (Chapman et al., 2010), while the motor cortex is responsible for movement execution, driving specific changes in gait modifications (Drew, 1988; 1993; Drew et al., 1996; 2002; 2008b). The resulting descending signals are ultimately sent to the spinal cord before a new movement is performed. Unlike in reaching where movements are usually ballistic and discrete, descending commands related to visuomotor adaptation must be superimposed onto spinal CPG networks producing the rhythm and pattern of muscle activity needed for walking, a continuous, non-ballistic task.

## 3.2. Limitations

There are a few limitations in this experiment that deserve consideration. These are summarized below.

A point for consideration in this experiment was that the protocols were created based on a Gaussian distribution of diopters and not the diopter differences from trial to trial. As a result, there could be large differences in the perturbations between protocols within the same condition or smaller differences between perturbations in different noise conditions. The former occurred if extreme lenses were placed next to each other more often in certain protocols than others, and the latter if the diopter differences in the low noise were similar to the diopter differences in the high noise. In addition, another limitation regarding our protocols was that some trials with extreme diopters might not have been perceived as high noise perturbations. For instance, if large diopters were preceded by one or more extreme diopters in the same direction (i.e., a 28 diopter followed by a 30 diopter), the net difference between them is low. Regardless these details regarding our protocol, it is important to emphasize that we used a randomization of lenses to manipulate uncertainty. Our significant baseline movement error variability and the adaptation residual RMSE effects across all the experimental noise conditions (see results) indicated that our distribution of diopters was sufficient to create the proposed uncertainty conditions. In addition, Figure 16 shows that the relationship between errors and diopter differences also follow a similar pattern as the relationship between errors and diopter sizes (Figure 15), in which errors increase with diopters and diopter differences.



**Figure 16. Relationship between errors and dioptric differences.**

Relationship between errors and dioptric differences. Errors were grouped in clusters that represented their trial orders in each protocol. Errors that A shows no noise baseline, D no noise adaptation, B low noise baseline, E low noise adaptation, C high noise baseline and F high noise adaptation. Errors of a dioptric with a higher saturation appeared early in a protocol and errors with lower saturation appeared later in a protocol.

Another limitation of this study was that diopters of different magnitudes might have been perceived differently, affecting subsequent movement errors. In particular, previous work by (Jakobson and Goodale, 2003) found that subjects that were exposed to diopters as small as 5 were not able to consciously perceive the visuomotor perturbations and had pointing errors not different than in control trials with 0 diopters. Thus, it could be argued that the small diopters used in our experiment were not sufficient to elicit a visuomotor perturbation or create visuomotor mapping uncertainty. In this study, small diopters within a  $\pm 4$  range were included in the total diopters used in the baseline and our results show that the baseline movement error variability was still significant across all noise conditions (see results). This result indicates that even small when combined to the range of diopters we defined in each uncertainty condition elicited visuomotor perturbations and created uncertainty. In agreement with these results, (Jakobson and Goodale, 2003) also showed that small diopter caused aftereffects,

which is an evidence that small diopters are also capable of eliciting motor compensations that are carried over to subsequent trials.

The contribution of other sensory systems to the adaptation process is also arguable in this study. In particular, previous research has also investigated the contribution of proprioception recalibration in visuomotor adaptation paradigms (Cressman et al., 2010; Reuschel et al., 2010; Cressman and Henriques, 2011; Reuschel et al., 2011; Salomonczyk et al., 2011; Henriques and Cressman, 2012; Salomonczyk et al., 2012). Overall, these studies show that visuomotor adaptation and learning are driven by information available from vision and proprioception. Thus, it is likely that our subjects were also recalibrating proprioception estimates to guide walking from trial-to-trial. To increase the demands of vision during the performance and avoid learning of a specific stepping sequence, we randomized the starting positions from trial-to-trial. Thus, given the goal of the task the subjects were forced to look through the lenses to localize the target every trial. Our results show a gradual increase in errors by diopter magnitude (see Figure 16) and large aftereffects across all noise conditions. These results indicate that our experimental paradigm in fact created a vision based task. Further studies could address this limitation by creating and validating a proprioceptive test for this type of paradigm in order to measure the contributions of vision and proprioception.

Most of the research studying error-based visuomotor adaptation was done with limited or no vision available during the movement (Körding and Wolpert, 2004; Wei and Körding, 2010). This procedure was done to avoid online corrections that could affect the movement responses regardless of the visuomotor perturbation. The walking task in this study was performed with the eyes open and thus a point of concern could be whether our movement error measurements were weakened by online corrections. Although we cannot rule out the possibility that online corrections affected some of the trials, this experiment was designed to reduce those effects. First, participants performed all experimental conditions in a room with reduced lighting condition, which in turn reduced any environmental references that could facilitate online corrections. By reducing environmental references, we limited the information of limb trajectory error to a target, which could lead to sudden corrections prior to arriving to the target. In addition, subjects

were asked to walk faster than normal and to avoid any sudden reductions of speed near the target area. This instruction prevented further online corrections throughout the experiment. Observation during the experiments and visual inspection of limb trajectory profiles also supports the notion that online corrections were absent. Finally, it must be considered that this limitation is a trade-off between movement functionality and a research-controlled environment. Given the importance of vision for walking, it may not be functionally relevant to perform the walking paradigm with the eyes closed.

In this experiment, we assumed that each experimental condition was independent of the other. This is because all subjects performed all experimental noise conditions in a randomization design, with conditions being always opposite in the magnitude to the previous condition. Adaptation to opposite rotations diminishes the contributions of learning of the first visuomotor relationship overtime (Krakauer et al., 2005; Krakauer and Shadmehr, 2006; Criscimagna-Hemminger and Shadmehr, 2008; Krakauer, 2009; Shadmehr et al., 2010). However, given that this process of learning may change in face of many factors and cause different consolidation and interference profiles, it is likely that we had different contributions of learning throughout this experiment. Although it is not possible to determine the contributions of learning and amount of interference in this experiment, our randomization design greatly reduced this confound and importantly, allowed for a within-subject design.

### **3.3. Directions for Future Research**

Our research investigated and established important mechanisms for how the nervous system tackles the problem of uncertainty to control and adapt walking. This project proposes that a common framework can explain the control of reaching and walking. This similarity in control expands questions for future research, some of which are summarized below.

Generalization studies have provided important insights into how adaptation is encoded across a variety of movement tasks and environments. Previous studies have suggested that generalization of reaching movements is a function of the statistics of previous practice (Krakauer et al., 2006) or is a function of how the nervous system estimates the sources of errors on the basis of uncertainty (Berniker and Körding, 2008). In the context of walking, conversely, Alexander et al. (2011; 2013) reported asymmetric generalization across different walking tasks. Thus, according to these views, investigating how sensorimotor uncertainty changes the generalization profiles during walking also brings important insights into the functioning of internal models when generalizing to different contexts and tasks. A question of interest is whether generalization during walking also happens as a function of the statistics of prior experiences, and whether uncertainty can better explain generalization patterns.

How visuomotor mappings are stored and learned has also been of particular interest for understanding how learning is encoded. Research in reaching has demonstrated that the learning of visuomotor mappings in reaching movements is subject to interference, such as when adapting to multiple conflicting visuomotor mappings. In addition, visuomotor mappings undergo a process of consolidation. That is, it become resistant to interferences with the passage of time or increased practice (Krakauer et al., 2005; Krakauer, 2009). Questions regarding how uncertainty and movement error variability play a role in the formation of motor memories have also been of particular interest in the reaching literature (Herzfeld et al., 2014). If sensorimotor uncertainty determines adaptation during walking, it is likely that these effects would be reflected during learning over time. This line of research provides new insights on the mechanisms of consolidation of motor memories. In particular, this is an essential step

towards understanding how the learning is encoded and the conditions that would be resistant to interferences across a great variety of motor tasks. Learning and memory are critical topics to rehabilitation, especially in the context of walking. For instance, efficient rehabilitation strategies need to be retained and transferred to multiple environments and effectors.

Research investigating the rate of visuomotor adaptation also report that different types of uncertainty, such as feedback, state estimation, visuomotor mapping and environment uncertainty, modulate the rates of adaptation differently in reaching movements (van Beers et al., 2002; Burge et al., 2008; Wei and Körding, 2010; Castro et al., 2014). Thus, to further identify how uncertainty modulates human adaptation in general, subsequent conditions needs to attempt to investigate the roles of different types of uncertainty in the adaptation during walking. These would include feedback, state estimation, and visuomotor mapping uncertainty.

In addition, there is an increasing interest in the research community for neurophysiological measures that can elucidate the role of different brain regions involved in adaptation and learning. Research in patient populations, with brain stimulation, using neuroimaging, and single and multiple cell recordings in non-human primates have provided importance evidence for how the brain works to control and adapt movements (Krakauer et al., 2004; Graydon et al., 2005; Newport and Jackson, 2006; Danckert et al., 2008; Luauté et al., 2009; Chapman et al., 2010; Bédard and Sanes, 2014). However, the majority of the literature is still based on arm and/or hand movements. Extending this to walking is an important future goal.

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