AN INVESTIGATION OF MOTOR MEMORY DEFICITS IN PARKINSON'S DISEASE

by

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ABSTRACT

People with Parkinson's disease (PD) display motor memory deficits when tested on motor adaptation tasks involving visuomotor rotations, while the process of adaptation itself seems largely unaffected. Other forms of adaptation are unexplored and the mechanisms underlying their motor memory deficits unknown. Previous research has suggested reinforcement mechanisms to be affected in PD, but whether defective reinforcement is underlying motor memory impairments has never been directly investigated. Firstly, we investigated if the motor memory deficits shown by earlier studies also hold for force-field adaptation, where the participant learns to compensate for a perturbation caused by an external force acting on the limb. We then explored if adaptation to such force-fields was possible when adaptation was dependent on contextual cues, i.e. if people with PD were able to make context-motor associations, and in addition we investigated whether augmentation of reward and punishment improved reinforcement in PD. To increase our understanding of the effect of reward and punishment feedback on context-dependent motor learning their separate effects were investigated in a group of young adults. Results showed intact recall of the learned adapted state in people with PD, suggesting intact consolidation, but motor memory as tested with interference, where memory of the initial adaptation impairs learning of an opposite adaptation, to be strongly reduced in PD. We found evidence that people with PD were less able to learn context-motor associations in comparison to older Controls and these deficits became more pronounced when success-based feedback was strengthened suggesting reduced sensitivity to augmentation of reward and/or

punishment. In young adults, reward and punishment feedback did not influence context-dependent motor adaptation itself, but it had some effect on movement velocity. We conclude that PD pathology leads to weaker context-motor associations and defective reinforcement processes, which may be underlying impaired recall of certain motor states.

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1

General Introduction

1.1 Motor Control

Throughout life we acquire many motor skills that, in some cases, can stay with us for the rest of our lives. In childhood we develop gross motor skills like walking, cycling, and kicking a ball, to more finer skills such as tying laces and writing. While our body grows we maintain these skills, despite the fact that the physical dimensions of our body change, as adjustments take place that generally go unnoticed. Perhaps even more interestingly the sensorimotor system is able to overcome sudden changes in our environment by rapidly adapting to new circumstances. We are able to switch between objects and devices with different shapes, weights and measurements, such as carrying out work on different computers or using hammers or tools of different weights. The process of gradual improvement of motor performance in response to altered conditions is called *motor adaptation* (Shadmehr, Smith, and Krakauer 2010; Krakauer and Mazzoni 2011).

1.1.1 Motor Adaptation

Motor adaptation can be studied in laboratory settings by exposing participants to perturbations to the sensorimotor system and measuring how well they overcome these changes. The visuomotor rotation (VMR) task is an example of a task to study motor adaptation, which can be performed with a joystick (Krakauer 2009). The participant is asked to move to eight (or less) targets located in a circle from a central position, while the cursor output is rotated 45 degrees, see figure 1.1A. Due to the rotation the participant miss the target (initially by an error similar in size to the imposed rotation) and needs to

adjust its motor output in order to successfully reach the target. Implicit adaptation to the rotation is not instant, but a gradual process that happens over a number of trials (Mazzoni and Krakauer 2006).

Force-field adaptation is also frequently used to study motor adaptation. Similar to the VMR task the participant is required to move between a starting point and a target or targets. However, instead of a rotation the motor output is perturbed due to a force-field acting on the handle with which the participant is moving through space to control the cursor (Shadmehr and Mussa-Ivaldi 1994; Scheidt et al. 2000), see figure 1.1B. In order for the participant to reach the target it needs to adapt to the force-field, which requires pushing against the field. Both the VMR and force-field task involve adaptation, but while force-field adaptation is a form of dynamic adaptation the VMR task is a form of kinematic adaptation. Dynamics is characterized by the study of motion due to forces acting on the object. Kinematics on the other hand analyses the motion of an object or point without considering forces. Kinematic adaptation is suggested to rely on an extrinsic coordinate system, often derived from errors obtained from the visual workspace, while dynamic adaptation is thought to also involve an intrinsic coordinate system, which is built on proprioceptive error (Krakauer, Ghilardi, and Ghez 1999). Both tasks have offered great insight into the process of adaptation, but it has been suggested that there might be different neural processes underlying these two forms of adaptation (Crutcher and Alexander 1990; Rabe et al. 2009; Krakauer, Ghilardi, and Ghez 1999; Jansen-Osmann et al. 2005; Flanagan et al. 1999; Riehle and Requin 1995).

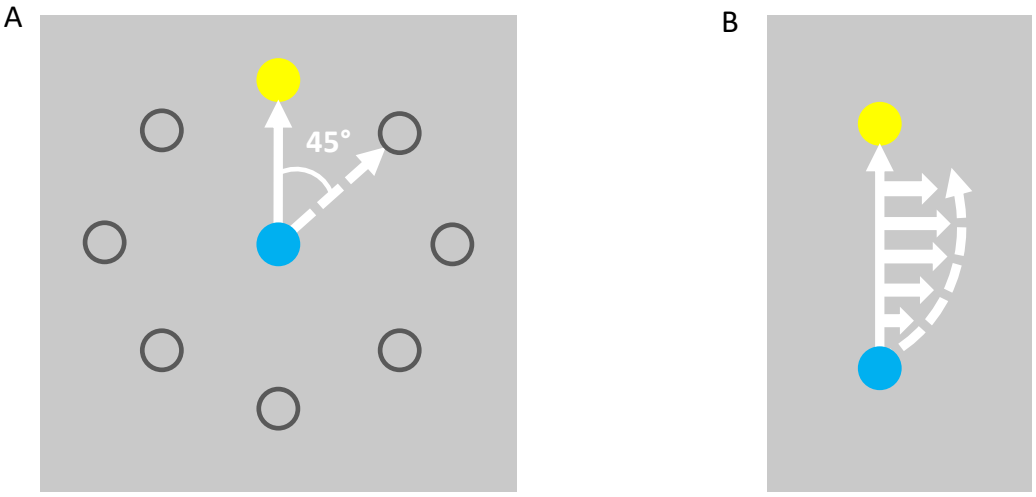


Figure 1.1 Motor adaptation using a VMR task (A) and force-field task (B). During a VMR task the cursor is rotated by 45 degrees, while during a force-field task the cursor is perturbed according to a viscous curl field (in this case in the clockwise direction). The solid white arrow represents the desired movement, while the dotted arrow is the perturbed movement.

1.1.2 Cerebellar-dependent process underlying adaptation

The goal of motor adaptation is to reduce the difference (i.e. the error) between the actual motor output and desired motor output, so to overcome any misalignment that is present due to a change in the environment. The cerebellum has been identified as the main structure driving adaptation. Patients with lesions in the cerebellum and cerebellar degeneration show deficits of motor adaptation (Straube et al. 2001; Maschke et al. 2004; Smith and Shadmehr 2005; Tseng et al. 2007; Golla et al. 2008; Gibo et al. 2013; M Panouillères et al. 2013; Panouillères et al. 2017). Similarly, reduced adaptation is shown by primates with experimental lesions of the cerebellum (Barash et al. 1999; Optican and Robinson 1980). Additionally, performance during adaptation tasks have been shown to

be affected when activity of the cerebellum was inhibited or enhanced using non-invasive brain stimulation (Jenkinson and Miall 2010; Galea et al. 2011; Panouillères et al. 2012; Herzfeld et al. 2014; Panouilleres, Miall, and Jenkinson 2015).

1.1.3 Forward Model

A crucial concept in how we think adaptation takes place is the forward model. When a participant is adapting to a perturbation they will initially miss the target. The sensory error between the executed and desired movement is used by the brain to improve the next movement. It seems that online sensory feedback is not used for adaptation, instead the signal used to drive adaptation is the error/sensory state at the end of the movement which is fed into an internal model that compares it to the brain's own estimate of the sensory feedback (Miall and Wolpert 1996). Information travels through our axons at a relatively slow speed, therefore the direct use of the sensory feedback to update motor output online would lead to unacceptable feedback delays that cause inappropriate fluctuations in movement corrections (Shadmehr, Smith, and Krakauer 2010). When a motor command is planned a so-called forward model uses the efference copy of the motor command and the current state of joint angels and velocity to predict the consequences of the motor command, which can occur before any sensory feedback is available (Miall and Wolpert 1996). Therefore, instead of having to rely on delayed sensory feedback a new motor command can be created based on the estimate of the sensory feedback. The difference between the observed sensory error and the predicted sensory error is called the *sensory prediction error* (SPE), which is used to update the

forward model (Shadmehr, Smith, and Krakauer 2010). Not only does the forward model overcome the issue of delayed sensory feedback it also results in a better internal representation of the world as the combination of the predicted and observed sensory state improves our perception (Miall and Wolpert 1996; Kawato 1999; Shadmehr, Smith, and Krakauer 2010). The efference copy of the motor command that the forward model uses could come from an inverse model, which calculates the required motor commands from the current and desired state of the limb (Miall et al. 1993; Kawato 1999). Empirical evidence supports the existence of a forward model (Wolpert et al. 1995; Kawato 1999) and shows it lies within the cerebellum (Miall et al. 2007; Tseng et al. 2007).

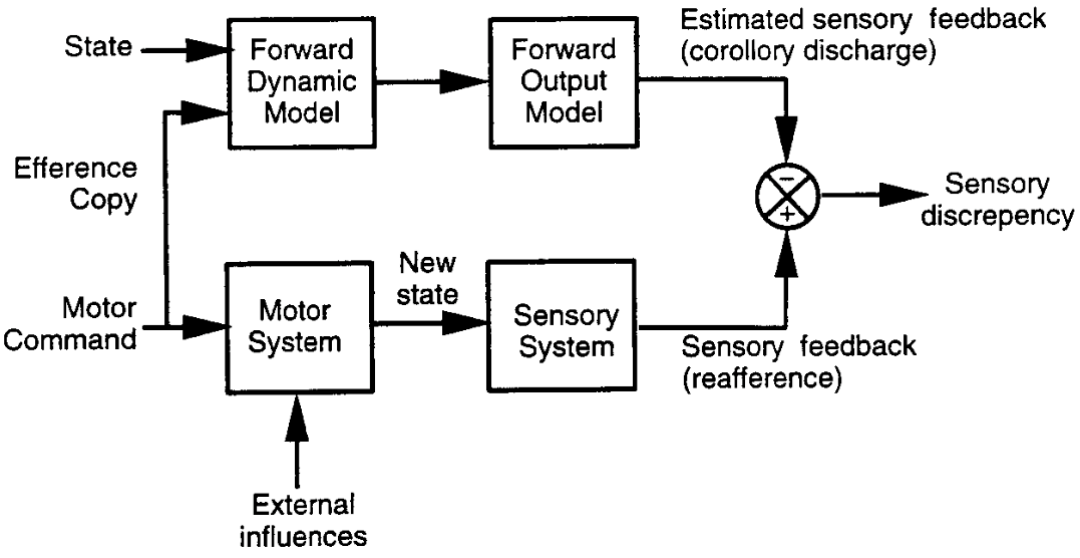


Figure 1.2 Diagram showing how the forward model generates an estimate of the sensory feedback from the efference copy and current state (top row). The bottom row shows the actual sensory feedback coming from the motor system. The sensory discrepancy (i.e. sensory prediction error) can inform the CNS about sensory afferent signals (those resulting from environmental influences) and provides a training signal for motor learning. From Miall and Wolpert (Neural Networks, 1996).

1.2 Motor Memory

Memory refers to the neural process that retains information or knowledge after acquisition and the ability to retrieve such stored information. Memory has been classified into two categories (Milner, Squire, and Kandel 1998); declarative memory and non-declarative memory. Declarative memory is a form of memory that can be consciously and intentionally recalled, this can be further separated into semantic memory (recollection of facts) and episodic memory (recollection of events). Non-declarative memory is a type of memory that is acquired and recalled unconsciously; it is gathered through changes in performance that are induced by experience (Gabrieli 1998). Procedural memory is a type of non-declarative memory where motor or cognitive skills are attained gradually through practice (Saint-cyr, Taylor, and Lang 1988). Memory that is formed after motor learning (which is part of procedural learning), such as acquiring a motor skill or motor adaptation, is often referred to as *motor memory* (Krakauer and Shadmehr 2006). The terms explicit and implicit learning are also often used to indicate the conscious/declarative and unconscious/non-declarative processes involved in learning and memory. While motor adaptation is thought to occur on-the-whole implicitly (Mazzoni and Krakauer 2006), recent studies have indicated that explicit processes can also be involved (Taylor and Ivry 2011; Taylor, Krakauer, and Ivry 2014; Mcdougle, Bond, and Taylor 2015).

1.2.1. Retention, savings and interference

When exposed to a perturbation the SPE increases initiating an update of the internal forward model (Shadmehr, Smith, and Krakauer 2010). A new relationship between the sensory input and motor output is learned to overcome the misalignment and reduce error. However, when the perturbation is removed the updated internal model is no longer accurate and error returns – this is commonly called an *aftereffect* (Shadmehr and Mussa-Ivaldi 1994). In VMR and force-field tasks this retention can be shown by a deviation in the opposite direction as the error during adaptation. The presence of this aftereffect indicates that a new sensorimotor mapping has been formed following the adaptation process and the retention as measured during such a washout phase tends to decay so that error returns to baseline levels over a number of trials (Davidson and Wolpert 2004; Kitago et al. 2013).

However, the adapted state can be retained in memory even after retention of the adapted state has been washed out by relearning the original (un-perturbed) condition. For example, when participants are re-exposed to the same perturbation following wash-out improved adaptation is often shown (Brashers-Krug, Shadmehr, and Bizzi 1996; Krakauer, Ghilardi, and Ghez 1999; Caithness et al. 2004; Krakauer, Ghez, and Ghilardi 2005), reflected by a smaller error and a steeper learning curve in comparison to the initial adaptation. The improvement during secondary exposure indicates that the adapted state has been consolidated to memory and is referred to as *savings*. However, savings are reduced when a counter perturbation (B) is performed between the initial (A_1) and secondary (A_2) exposure, such as is the case in a A_1-B-A_2 paradigm (Robertson, Pascual-

Leone, Miall 2004). Adaptation to the counter perturbation B destabilizes the formation of memory of A_1, resulting in less improvement during A_2 compared to an A_1A_2 paradigm. This phenomenon of *retrograde interference* reduces savings (Brashers-Krug, Shadmehr, and Bizzi 1996; Shadmehr and Brashers-Krug 1997; Krakauer, Ghilardi, and Ghez 1999; Caithness et al. 2004; Krakauer, Ghez, and Ghilardi 2005; Sing and Smith 2010). To complicate the picture further adaptation of the counter perturbation itself is also prone to *anterograde interference* as memory of A_1 makes it harder to adapt to B (Miall, Jenkinson, and Kulkarni 2004). This is for instance shown when two equal but opposite perturbations are learned in succession. A larger error will be maintained during adaptation of B. Similarly, anterograde interference exists between B and A_2.

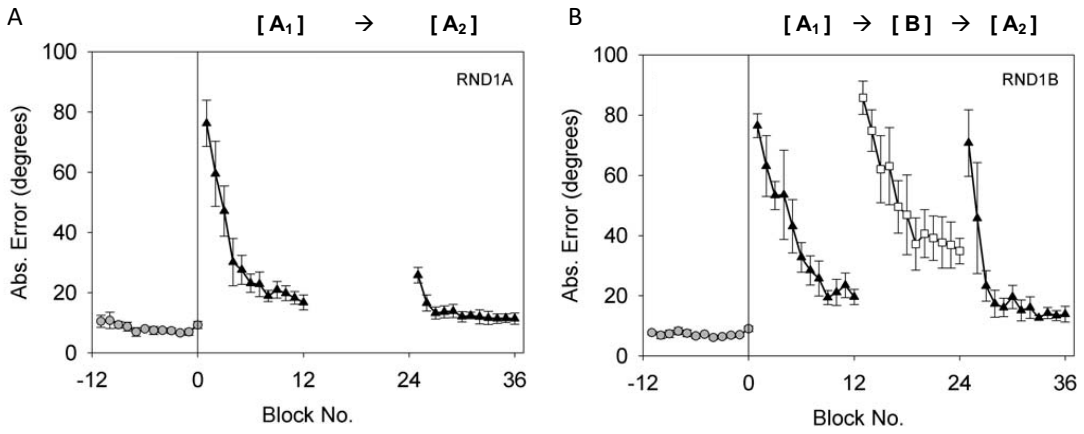


Figure 1.3 Group average of absolute error (in degrees) during a VMR task; from Miall, Jenkinson and Kulkarni (Exp Brain Res, 2004) *A) A_1-A_2 paradigm where improved error reduction is shown during A_2 indicating savings. B) Performance of an A_1-B-A_2 paradigm shows increased error during B compared to A_1 and higher error during A_2 compared to the A_1-A_2 paradigm indicating that both B and A_2 were affected by interference.*

1.2.2 Reinforcement

With passage of time savings of the initial adaptation (A_1) decline (Criscimagna-Hemminger and Shadmehr 2008), but the memory also becomes more stable so that it is protected against interference (Brashers-Krug, Shadmehr, and Bizzi 1996; Shadmehr and Brashers-Krug 1997). When time between A_1 and B is increased the effect of retrograde interference is reduced resulting in less disrupted performance of A_2 (Brashers-Krug, Shadmehr, and Bizzi 1996). However, anterograde interference also decays over time (Shadmehr and Brashers-Krug 1997) suggesting that not only memory of A becomes more robust, but also less of an influence to other newly learned adaptations. Retention of an adaptation also increases when training by repetition of the newly learned sensorimotor mapping is prolonged after asymptote is reached (Joiner and Smith 2008; Inoue et al. 2015).

Huang *et al.* (2011) argued that two model-free processes are involved in motor adaptation and explain the presence of retention and savings. They reasoned that retention was caused by *use-dependent plasticity*; a process where directional bias is induced by the repetition of a new alignment in hand space. In addition, they argued that for savings to take place a process of *operant reinforcement* needs to link the new sensorimotor mapping to successful outcome such as a decline in error. The latter process is related to operant/instrumental conditioning, where behaviour is strengthened when it is followed by a reward (and weakened when followed by punishment). The exact underlying processes of operant reinforcement remain unknown, but it has been shown that adaptation in the absence of visual error is possible using success-based/operant

mechanisms (Izawa and Shadmehr 2011; Shmuelof et al. 2012) and that increased reward leads to more retention of the adapted state (Shmuelof et al. 2012; Galea et al. 2015; Nikooyan and Ahmed 2015; Song and Smiley-Oyen 2017).

1.2.3. Involvement of the Motor Cortex

Several studies suggest that memory of the adapted state is stored in the motor cortex (M1). Disruption of this area using transcranial magnetic stimulation (TMS) leads to reduced after-effects (retention) (Hadipour-Niktarash et al. 2007) and diminished savings (Richardson et al. 2006). Also Galea et al. (2011) showed that stimulation of M1 with anodal transcranial direct current stimulation (aTDCS) increased retention after adaptation. The same study showed that participants who received this stimulation over the cerebellum instead showed better adaptation, which implies that activity shifts from the cerebellum to the motor cortex after adaptation. However, Panouillères et al. (2015) found no effect on retention when stimulating M1 using tdcs, but adaptation itself improved. Similarly, no benefits of M1 stimulation on retention were found by Herzfeld et al. (2014). Although M1 involvement in motor memory is likely more research is needed to clear up the discrepancy currently present in the literature.

1.3 Basal Ganglia Involvement in adaptation: Insights from Parkinson's Disease

1.3.1 Basal Ganglia anatomy and function

The Basal Ganglia (BG) is a group of subcortical nuclei comprising the striatum (caudate and putamen), globus pallidus (internal and external segments; GPi and GPe), substantia

nigra, and subthalamic nuclei (STN). The substantia nigra can also be separated into two segments; pars reticulata (SNpr) and pars compacta (SNpc). The striatum receives input from the cortex after which it is projected and processed within the rest of the BG before the output is sent back mainly to the cortex via the thalamus, with other output to several nuclei of the brainstem including the superior colliculus (SC) and the pedunculo-pontine nucleus (PPN). There are two major pathways through the BG; a *direct pathway* and an *indirect pathway*. A smaller hyper direct pathway also exists, which bypasses the normal input to the BG, the striatum, and projects directly to the STN which is proposed to rapidly inhibit unwanted movement. Figure 1.4 shows the direct and indirect pathway. The direct pathway (also referred to as the GO pathway) is considered an excitatory pathway promoting action, e.g. a movement or response, while the indirect pathway (NO GO pathway) promotes inhibition.

Historically the BG has been mainly implicated in motor behaviour, but later research has demonstrated that the BG are involved in a wide variety of functions, in both the motor and non-motor domains. With use of the different pathways the BG is thought to help with action selection; it selects an action from a set of options while suppressing irrelevant brain activity (Redgrave et al. 2010). The BG also has a prominent role in implicit learning and memory, in particular the acquiring of stimulus-response (S-R) associations and habits (Packard and Knowlton 2002). Stimulus-driven behaviour is established through reward-based processes; where the bond between a stimulus and a response is strengthened when the outcome is rewarding. Lesions of the BG in animals prevents the ability to learn or execute actions in order to gain a reward or avoid

punishment (Yin and Knowlton 2006). Dopamine is the important neuromodulator in BG-driven reward-based learning as it facilitates reinforcement of actions through signalling of a reward-prediction error (RPE), i.e. the difference between the expected and received reward (Schultz 2016). When RPE is positive, i.e. reward is higher than expected, dopamine signals increase, when RPE is negative, i.e. reward is lower than expected, dopamine will decrease, and when the expected and received reward match dopamine will remain at baseline levels (Schultz 2002). More recent evidence suggests that the BG has a dynamical interplay not only with cortical areas, but also with the cerebellum, making up a cerebellar-basal-ganglia-cortical system. In this framework the BG is thought to be specialised in reinforcement learning, while the cerebellum and cortical areas displays supervised and unsupervised learning, respectively (Caligiore et al. 2017).

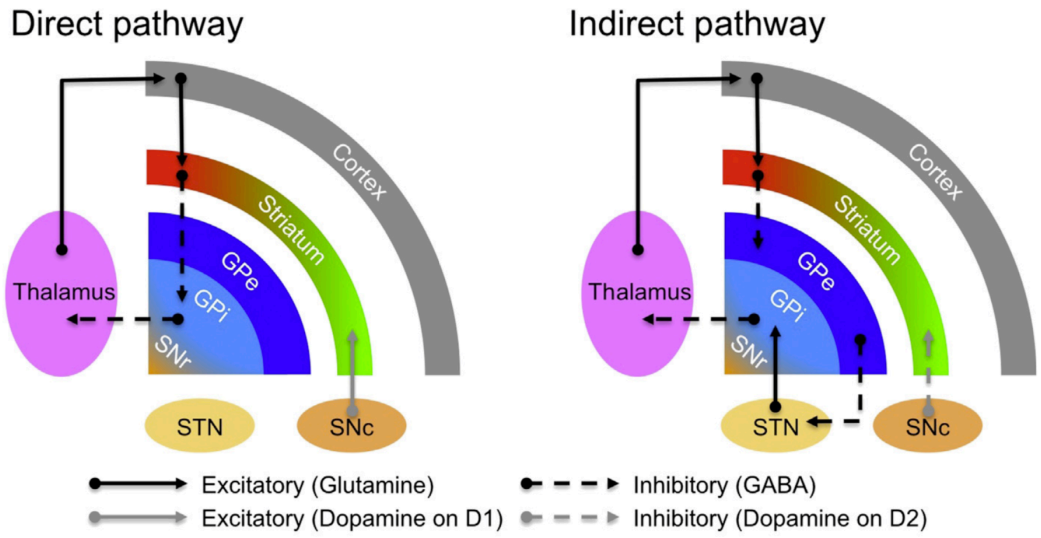


Figure 1.4 Direct and indirect pathway of the Basal Ganglia. From Watkins & Jenkinson (Neurobiology of Language, 2016). The direct pathway releases the tonic inhibition exerted by the thalamus therefore allowing initiation of movement. In contrast, the indirect pathway increases the tonic inhibition therefore reinforcing suppression of movement.

1.3.2 Parkinson's disease

Parkinson's disease (PD) is neurodegenerative disorder that is most commonly known for its motor deficits. PD is caused by pathology in the SNpc where degeneration of the dopaminergic (DA) cells takes place. Dopaminergic projections from these cells innervates the striatum where it is involved in the inhibition and excitation that occurs between the structures that make up the BG. The BG helps maintain motor control through the direct pathway, which promotes movement, and the indirect pathway, which inhibits movement. The degeneration of the DA cells in PD leads to a depletion of dopamine in the striatum with as result an overactive indirect pathway, causing among things increased suppression of movement.

PD is most obviously characterized by the motor symptoms of tremor, bradykinesia, rigidity, and postural instability, but can also involve other symptoms such as freezing, masked face and slurred speech, though it is becoming more accepted that people with PD can also display cognitive deficits (for review see Robbins and Cools, 2014). Medication can alleviate the motor symptoms that PD sufferers experience. Levodopa, a precursor of dopamine, is still the most common treatment for PD as it replenishes the shortage of dopamine in the brain. Other medication often prescribed are dopamine agonists that target the DA receptors. PD can also be treated with deep brain stimulation (DBS), which involves the neurosurgical insertion of electrodes into the STN or GPi. Though there is some success in treating PD through these measures, the reason why dopamine cells in the SN die in PD remains unknown.

1.3.3 Motor memory problems in PD

Despite problematic motor control in PD, adaptation to VMR or prisms, i.e. kinematic adaptation, was found to be mostly intact (Stern et al. 1988; Fernandez-Ruiz et al. 2003; Marinelli et al. 2009; Bédard and Sanes 2011; Isaias et al. 2011; Leow, Loftus, and Hammond 2012; Gutierrez-Garralda et al. 2013; Leow et al. 2013) therefore suggesting cerebellar-dependent adaptation processes to be unaffected. However, several studies show that consolidation after adaptation to a VMR impaired is in PD as studies showed reduced savings (Marinelli et al. 2009; Bédard and Sanes 2011; Leow, Loftus, and Hammond 2012) and diminished interference (Leow et al. 2013). Moreover, how adaptation to dynamic perturbations is affected in PD has only been investigated by one study (Krebs et al. 2001), which showed altered interference and adaptation. These results suggest an important role of the BG in consolidation and possible involvement in adaptation to dynamic perturbations, one that requires further investigation. In Chapter 3 we carried out a thorough investigation of force-field adaptation in PD. Savings and interference were tested after 1-hour and after a night of sleep. Chapter 2 holds a summary of the analysis used to explore savings and interference of force-field adaptation.

Earlier research has also shown that people with PD display problems with acquiring non-motor S-R habits (Saint-cyr, Taylor, and Lang 1988; Knowlton, Mangels, and Squire 1996; Ashby et al. 2003; Daphna Shohamy et al. 2005). The formation of habits is characterized by a process where a switch occurs from goal-directed actions to stimulus-driven behaviour, which is facilitated by operant reinforcement mechanisms (Yin and Knowlton 2006). The signalling of reward and punishment is thought to be

affected in PD. Frank et al. (2004) showed with two cognitive procedural learning tasks that the sensitivity to positive and negative outcome was altered in PD. As previously mentioned, consolidation of the adapted state is also thought to occur through the process of operant reinforcement, but if issues with operant reinforcement also underlie the motor memory deficits in PD after adaptation has never been directly investigated.

In Chapter 4, we investigated context-dependent force-field adaptation in PD with a task where two opposite but equal force-fields could be learned using field specific context. Performance could only improve when the context-motor association was learned, therefore this motor task shows similarities to tests on non-motor S-R associations in PD and allowed us to see whether consolidation of an adapted state in relation to its contextual cue was affected in PD. Using the same task we then enhanced reward and punishment to see how operant reinforcement on this motor task was affected in PD. In addition, to gain more understanding of the results we investigated the separate effects of reward and punishment on the context-dependent force-field task using a cohort of young healthy adults (Chapter 5).

1.4 Conclusion

By studying force-field adaptation in people with PD we hope to get a better understanding of how PD pathology impacts motor adaptation and motor memory and how the BG is involved in processes underlying dynamic adaptation and consolidation. In our first study we investigated to what extend force-field adaptation affected was in people with PD and if they displayed problems with motor memory similar as shown for

kinematic adaptation. We then investigated the ability of people with PD to learn two equal but opposite force-fields simultaneously using context and tested their sensitivity to augmented reward and punishment. Lastly, we tried to deeper our understanding of how reward and punishment during context-dependent force-field adaptation modulates performance using young adults.

Chapter 2

Analysing force-field adaptation using linear mixed effects models in R

2.1 Introduction

To test for dynamic motor adaptation in PD, force-field adaptation was used for the studies presented in this thesis. In order to accurately determine and compare performance of healthy controls and PD participants statistical analysis were performed using linear mixed effects (LME) models with the software R. This section starts with a brief summary on the methodological apparatus, the force-field task and the main measure outcomes that were acquired through data analysis with the software MATLAB. Then LME models will be discussed. Using data of younger adults I will demonstrate the benefits of using an LME model, where the adaptation is described by a 2-degree polynomial function and with carefully chosen random effects, over the more commonly used statistical analysis.

2.2 Methodological apparatus: Velocity-dependent force-field robot

Force-field adaptation was tested using a device that produced velocity dependent force-fields (vBot), similar to Howard et al. (2009). The core of the device consists of a motor with a robotic arm attached to it permitting 2D-planar movements. An aluminium frame was built around the device, which holds the motor as well as a semi-silvered mirror and a monitor. The frame is supported by a leg-structure that allows up and downwards movement of the frame so that the manipulandum could be positioned according to the participants height. The semi-silvered mirror overlays the manipulandum and loses its transparency when room light is dimmed eliminating vision of the hand and robotic arm itself. The monitor is placed above the mirror facing down, so that the display on the computer monitor is projected onto the mirror. The motor that controls the robotic arm

can generate torques that are transferred to the hand of the participant holding the robotic manipulandum. Optical encoders record the position of the handle with a sample rate of 1000 Hz. Participants sat in an armless chair holding on to the handle of the robotic arm and looking down on the mirror; see figure 2.1. The forehead of the participant was rested against a padded surface that was attached on the frame above the mirror. The position of the handle was shown to the participants as a circular cursor in real-time.

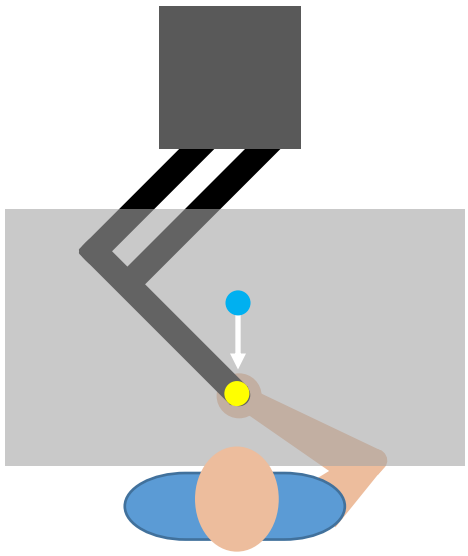


Figure 2.1 Velocity dependent force-field robot (vBot). Participants hold the handle of the robotic manipulandum and make reaching movements from a starting point (blue) to a single target (yellow).

2.3 Force-field adaptation task

The force-field task used in the studies of the following chapters consisted, unless otherwise specified, of a starting point in the centre of the mirror and a single target located 10 cm closer to the participant. Participants always performed the task with their

right limb. Before the onset of a trial both the starting point and target were displayed in grey. The participant was required to make an active movement with the handle from the starting point to the target, which was a 10 cm inward reach. In earlier studies that were carried out in our lab participants made a 20 cm reach outwards. However, during these studies some participants struggled to stop in the target despite instructions to do so, as the participants tended to make a vigorous ballistic movement of the arm that was hard to stop. Therefore, the task was reversed to an inwards reach as we hypothesized that participants would follow the instructions to stop in the target more easily because of an incentive to not punch their own body. This turned out to be the case. In addition, to accommodate the PD patients and elderly the reach was shortened; from 20 to 10cm. When the target was reached, participants were asked to hold on to the handle which was then automatically guided back to the starting point by the robot, therefore this movement was passive.

Participants were asked to make straight lines from the starting point to the target while being exposed to two scenarios (see figure 2.2). Either the vBot imposed a force-field on the handle, which required the participant to counteract (i.e. adapt) to reach the target in a straight line. Or no forces were applied, i.e. the participant experienced a null field. The force was a viscous curl field acting in the clockwise (CW) or counter clockwise (CCW) direction and was velocity dependent with a strength of 12 N/m/s (see equation 2.1).

$$\begin{bmatrix} F_x \\ F_y \end{bmatrix} N = \pm \begin{bmatrix} 0 & 12 \\ -12 & 0 \end{bmatrix} N \cdot s/m \begin{bmatrix} V_x \\ V_y \end{bmatrix} m/s \qquad \text{[eq. 2.1]}$$

Generally, the task comprised of four phases; a baseline, adaptation, washout, and re-adaptation phase. During baseline and washout no forces were applied, while the adaptation phases were tested with the forces on. The baseline phase allowed participants to get used to the vBot and task and provided baseline measurements of performance. The phases with the forces on provided insight into the ability to adapt to a novel force-field (first adaptation phase) and improvements shown when re-exposed (re-adaptation). The removal of the force-field after adaptation (washout phase) allowed measurement of retention of the new sensorimotor remapping and returned participants to baseline levels before retesting.

On most trials the actual real-time position of the cursor was shown, but occasionally an *error-clamp trial* was implemented. An error-clamp trial is a trial in which the error (hand displacement) is clamped at zero (spring coefficient = 5000 N/m, damping coefficient = 30 N · s/m) and therefore prevents the participant from moving sideways, i.e. the participant is forced into a straight line to the target. The exact cursor location is not shown during such an error-clamp trial. Instead, the distance from the target is indicated with a semi-circle that expanded from the starting point so that a measure of distance to the target was given but not the exact position. Often participants report not being aware of the clamp and perceive the trials as being the same as the 'normal' trials but with limited feedback. During an error-clamp trial the force that the participant imposes on the clamp is recorded and can be used as an additional measure of learning (see section about Force Compensation below). More force imposed on the clamp indicates a stronger compensation to the force-field.

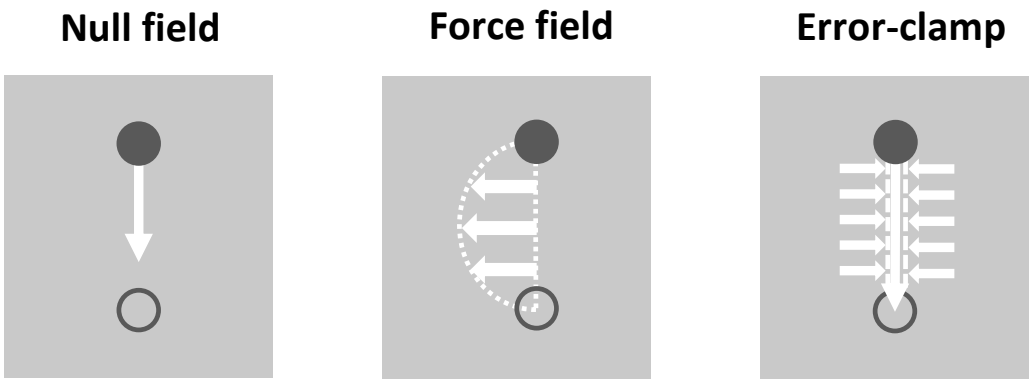


Figure 2.2 Different conditions experienced during an adaptation task. Participants make reaching movements from the starting point (dark grey) to the target (open grey circle). During a null field no forces are imposed on the handle, while during adaptation the participant experiences a force-field (in this case in the clockwise direction). An error-clamp trial forces the participant in a straight line to the target due to perpendicular forces on the direction of movement (white arrows). During an error-clamp trial the participant sees a semi-circle expanding from the starting point indicating their distance to the target (not shown in figure).

2.4 Lateral Deviation at peak velocity as measure of hand displacement

The force-field imposed causes a lateral displacement of the participant's hand. The size of the displacement will reduce over time if the participant succeeds in compensating for the force-field. Figure 2.3 shows the cursor trajectory during 140 trials of force-field adaptation of a single participant. At the start, the deflection is large (blue lines) and then reduces to values closer to zero (indicated in red). Lateral deviation (LD) – the deviation perpendicular to the direction of movement – at the maximum velocity (also referred to as peak velocity) displays the reduction in error that takes place. LD provides an accurate representation of the initial displacement caused by the force-field and the adaptation that follows thereafter.

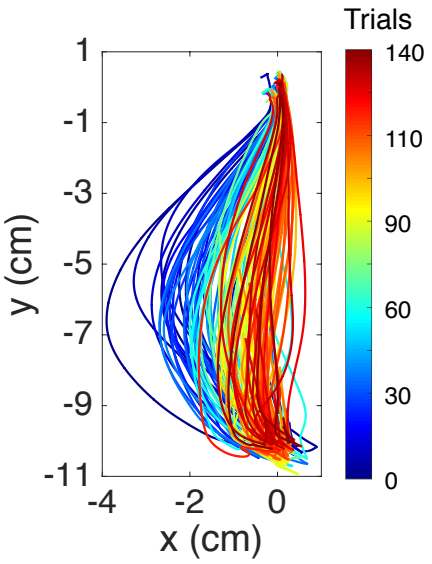


Figure 2.3 Hand trajectory of a single subject during adaptation to a CW force-field.

2.5 Force Compensation Ratio as index of adaptation

The LD represents one measure of how well the error is overcome during adaptation. In addition, adaptation to the dynamic properties can also be studied by measuring how well the participant is able to compensate for the force-field. Using error-clamp trials, which are interspersed among the normal trials, the compensatory force produced by the participant in absence of the imposed force can be measured, therefore giving a measure of the output of the motor system in the face of the imposed force-field. The compensatory force, hereafter referred to as the *actual Force*, is then compared to the force that should have been produced for full compensation, i.e. the *ideal Force*, see figure 2.4. In actuality the error-clamp trial does not impose a force, but due to the unpredicted nature of the error-clamp trial the participant still compensates for the force its expecting. The

magnitude of the expected force is related to the velocity of movement, see equation 2.1, and can therefore be calculated. Both the *actual* and *ideal Force* are integrated from t_0 till t_{end}, which is the first and last time point that the velocity goes above and below 4 cm/s, respectively, after which a ratio is computed according to equation 2.2 (similar to Howard et al., 2013).

$$FC\ ratio = \frac{\int_{t_0}^{t_{end}} actual\ Force}{\int_{t_0}^{t_{end}} ideal\ Force} \times 100\% \qquad \text{[eq. 2.2]}$$

The ratio represents the force compensation by the participant; 0% meaning no compensation, 100% suggesting full compensation. The amount of increase of the FC Ratio during the adaptation phases reflects the participants' ability to learn to adapt to the force-field. Force compensation should be zero for periods where no forces are applied, such as during the baseline and washout phase.

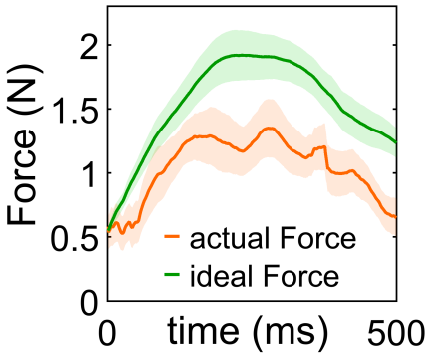


Figure 2.4 Sample data of an error-clamp trial. In orange the force produced by the participants (actual Force), in green the force that should have been produced for complete compensation of the force-field (ideal Force).

2.6 Statistics: Linear Mixed-Effects Models in R

The LD and FC of the adaptation (and de-adaptation) phases presented in this thesis were analysed using LME models in the software program RStudio Version 1.0.136 (R Core Team 2016). LME models are statistical models that include both fixed and random effects and have therefore some advantages over the more commonly used general linear models (GLMs), such as ANOVAs, which do not include random effects. In this section I will discuss why adding random effects can make results more accurate as well as explain the LME model used in my experimental chapters using data of younger adults.

2.6.1 Benefits of Mixed Models

A mixed model contains fixed effects and random effects, hence the term mixed, and is especially useful when dealing with repeated measurements. Mixed models can handle missing values as opposed to a repeated measure ANOVA where data sets with missing values are removed from the analysis, e.g. excluding an entire subject when one observation is absent (Gueorguieva and Krystal 2004). Fixed effects are mostly determined by the design of the experiment and tend to be of interest to the investigator (Baayen et al., 2008). For example, factors such as *group* (controls vs. patients) and *treatment* (day 1, day 2, day 3, …, day 5) are controlled by the researcher and therefore not considered to be random, but fixed. GLMs only include fixed effects, but data also tends to have some random variation that cannot be explained by fixed effects and is often caused by individual differences. Variation that is confounded with the effect of interest, but not included in the model can cause means to appear more different than they are and

therefore often increases the risk of Type I error (Barr et al. 2013). Type I error, also called false positive, is when the null hypothesis is rejected when in fact it was true. In addition, variation that is not accounted for and independent to the effect of interest often reduces power (Barr et al. 2013). With mixed models, individual differences can be used to describe some of the random variation in the data by the inclusion of random effects (Field, Miles, and Field 2012). Mixed models are therefore able to acknowledge both individual and group differences in the data and subsequently can improve the interpretation of the data (Krueger and Tian 2004).

With regards to the example given above (*group* and *treatment* as fixed effects), the use of an LME model over a GLM could both enhance power and reduce risks for false positives by defining a random effect that allows subject specific variation of both the intercept and slope in the model. However, including extra effects (random or fixed) does not necessarily mean that the model always becomes a better fit to the data (Bates et al. 2015). The coefficient of determination (R^2) will reflect if the addition of a fixed or random effect leads to enhancement of the explained variance. Also, overcomplicating a model without gaining little improvements is not recommended. The Akaike information criterion (AIC) and Bayesian information criterion (BIC) take in account the fit of the model and the number of variables included, so when comparing models these measures will provide an indication of which one is better (Vrieze 2012). A smaller AIC and BIC generally represent a better fit. BIC can be conservative as it tends to penalise complex models more. A likelihood ratio test (LRT) can be performed providing statistical

foundation for whether you should accept or reject the more complex model (Field, Miles, and Field 2012).

2.6.2 The LME model for force-field adaptation data

The LME models for the LD and FC data were built with the *lmer* function from the 'lme4' package (Bates et al. 2015) in R. To describe the adaptation curves a 2-degree polynomial function was used, which was commonly a better fit than an exponential function and seemed to describe our data well. The R-function *poly()* was used to generate polynomial functions with orthogonal predictors (Field, Miles, and Field 2012). Input for the polynomial function was a continuous variable with number of trials or blocks (average of trials). The LME models were fit by maximum likelihood with lmer and residuals inspected to determine suitability.

Hereafter, the fixed effects of the LME model were tested for statistical significance using the package 'lmerTest' (Kuznetsova et al. 2017). A type III Analysis of Variance table was generated including F-tests and p-values for the main and interaction effects. Degrees of freedom were calculated using the Satterthwaite's method. Significant interaction effects were further investigated by performing Bonferroni adjusted post-hoc analysis on the estimated marginal means using the package 'emmeans' (Lenth 2018).

2.6.3 Testing linear models using pilot data of Younger Adults

A group of young adults (N = 12, Age 27 ± 1, 9 females, 2 left-handed) performed a force-field adaptation paradigm using the vBot. They learned to adapt to a CW force-field (12 N/m/s) and after a 1-hour break and a period of washout were re-tested on the same CW force-field (see Chapter 3 for details about experimental protocol). In this example the focus will be on the LD data of the adaptation phases. The group-average of the LD at peak velocity is depicted in figure 2.5. As expected, participants successfully adapted to the force-field and the plot also indicates an improvement of LD reduction during re-adaptation. There is only one group in this example, so the dataset was used to see if there were any within-group differences between the first adaptation phase (Adapt 1) and the second adaptation phase (Adapt 2), in other words if the group displayed significant improvement in adaptation when re-exposed to the force-field, i.e. savings. Therefore, *phase* was the effect of interest. Both Adapt 1 and Adapt 2 consisted of 140 trials, which were averaged into 28 blocks of 5 trials (values outside the mean ± 2*SD were removed).

The results of four models will be discussed: (1) a linear model without random effects (fitted using the function *lm*) with fixed effects *phase* and *block*, (2) a linear model without random effects with fixed effects *phase* and an orthogonal 2-degree polynomial function generated with the R-function *poly()*; *poly(block, 2)*, which includes a slope (linear term, e.g. *block*) and curvature (quadratic term, e.g. $block^2$), (3) an LME-model (fitted with *lmer*) with fixed effects *phase* and *poly(block, 2)* and subject as random effect, and (4) an LME-model with *phase* and *poly(block, 2)* as fixed effects and a random effect that allowed between subject variation of the polynomial function for each phase. Model

specifics are shown in table 2.1. In model 3 and 4 subject is added as a random effect, but in model three only the intercept can change for each subject, while in model 4 both the intercept and slope/curvature can change for each subject and phase. The latter model therefore captures the subject-specific variation in adaptation, while the other models use a more generic approach.

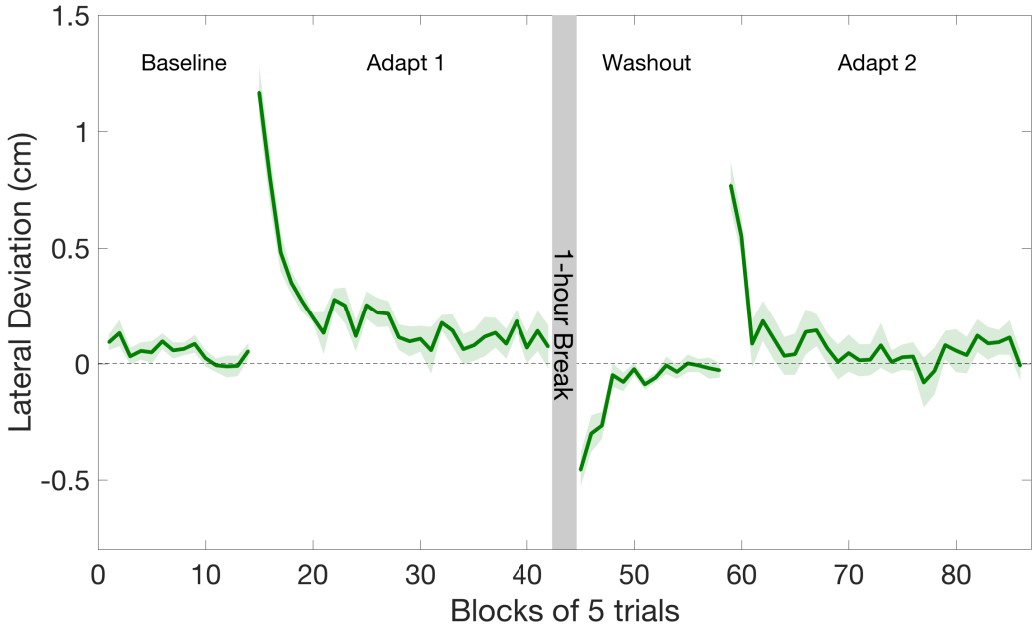


Figure 2.5 Pilot data of a force-field adaptation paradigm performed by young adults. Grouped LD data shown in blocks (average of 5 trials) for Baseline [block 1 – 14], Adapt 1 [block 15 – 42], Washout [block 45 – 58], and Adapt 2 [block 59 – 86].

Table 2.1. Summary of models tested and associated measures for model selection.

No.	Model syntax[1]	R^2	BIC	AIC
[1]	LD ~ phase × block	0.177	323.9	301.4
[2]	LD ~ phase × poly(block, 2)	0.285	241.9	210.3
[3]	LD ~ phase × poly(block, 2) + (1 | subject)	0.393	168.8	132.7
[4]	LD ~ phase × poly(block, 2) + (phase × poly(block, 2) | subject)	0.523	201.9	75.6

[1]for notation see Bates *et al.* (2015)

2.6.3.1 Model comparison

The calculated R^2 (see table 2.1) demonstrates that model 1 explains 17.7% of the variance. When a quadratic term is added for adaptation (model 2); *block* is replaced by *poly(block, 2)*, the variance increases to 28.5%. Figure 2.6 shows that while model 1 only captures the slope of adaptation model 2 also captures the curvature of learning. When *subject* is added as a random effect in model 3, such that the intercept may change, R^2 increases to 39.3%. Even though the LD comes from 12 subjects, model 1 and 2 treat all observations as if they were independent. However, when *subject* is added as a random effect a separate intercept is created for each subject leading to improvement of the fits. Figure 2.6 shows that for the simple lm-model (model 2) the polynomial functions are identical for all subjects leading to better fits on some individuals than on others. While the polynomial functions are still identical in model 3 some individual variation is introduced by an upwards or downwards shift of the two fits (Adapt 1 and 2 together) due

to the allowance of intercept change between subjects. However, in reality data coming from motor adaptation tends to be even more variable, i.e. the shape of the learning curve often differs between participants too, and can even be inconsistent between phases within subjects. Model 4 accounts for this individual variation by the inclusion of a random effect that allows the polynomial function to change for each subject and phase too; i.e. model 4 includes an intercept and linear and quadratic term of the polynomial function for each subject. Not only does this lead to an improvement of the explained variance, $R^2 = 0.523$, the fits are also noticeable better. In line with the discussed above AIC declined with increasing complexity of the model as shown in table 2.1; model 4 had the lowest AIC, while model 1 had the highest AIC. The BIC of model 3 was also lower than model 1 and model 2, but was higher for model 4 than model 3. To determine model selection a likelihood ratio test was performed, which revealed model 4 to be significantly better than model 3; $\chi^2(20) = 97.108$, $p < 0.001$.

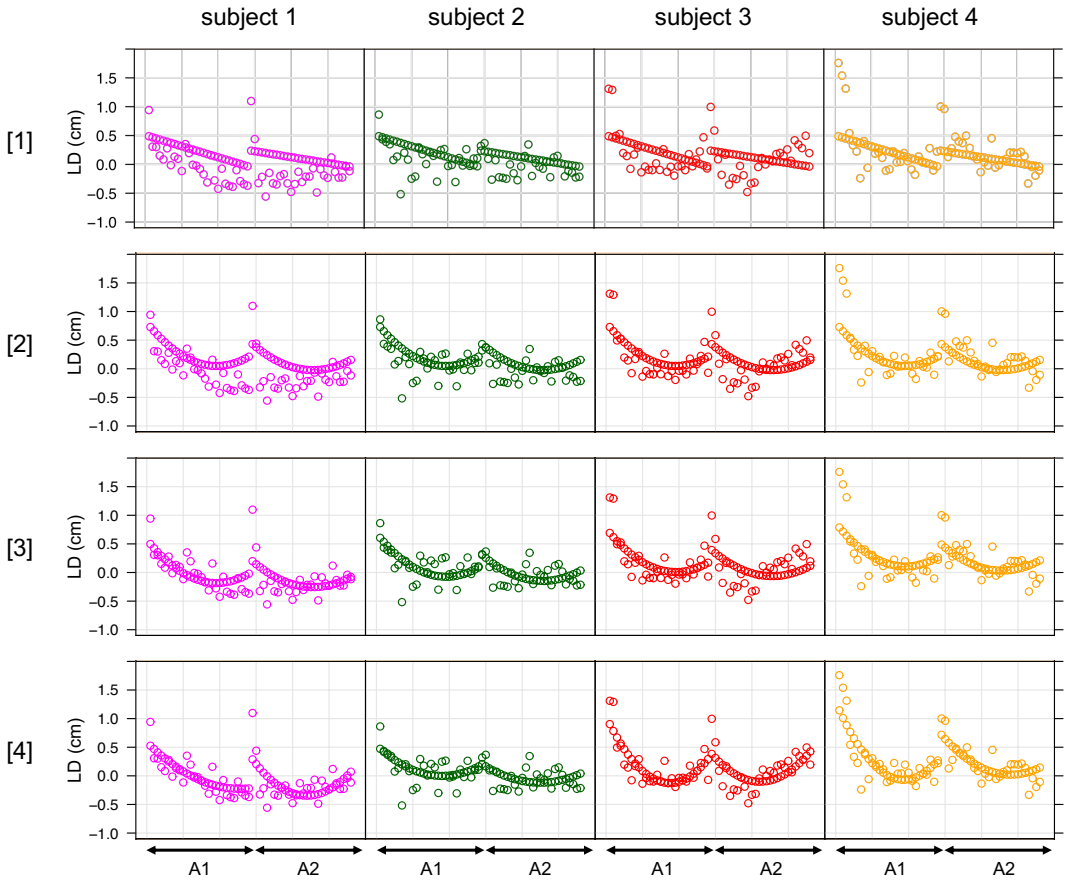


Figure 2.6 Fits of Model 1 – 4 shown with the actual LD data of 4 subjects for Adapt 1 (A1) and Adapt 2 (A2). The baseline and washout phase preceding A1 and A2, respectively, were not included in this statistical analysis and therefore not shown in the figure.

2.6.3.2. Results from Model 4

Firstly, the end of baseline and end of washout were inspected to make sure that the initial and secondary adaptation both started from similar baseline levels. The last two blocks of baseline (block 13 and 14) and the last two blocks of washout (blocks 57 and 58) were averaged and tested for significance using a mixed model including the fixed effect *phase* (baseline vs. washout) and the random effect *subject* (allowing subject specific variation

of intercept). No significant effect was found for phase; $F(1, 12.0) = 1.642$, $p = 0.224$, meaning that LD was comparable at the end of baseline and washout. Hereafter, F-tests were performed on the fixed effects of model 4 and revealed a significant main effect for *phase* (Adapt 1 vs Adapt 2); $F(1, 12.0) = 7.865$, $p = 0.016$, and for the polynomial function including *block*; $F(2, 12.2) = 31.039$, $p < 0.001$. A significant effect was also found for the interaction of *phase* × *poly(block, 2)*, in the following chapters for simplicity referred to as *phase* × *block*; $F(2, 12.9) = 4.522$, $p = 0.033$.

The results of this test dataset show that young adults display savings after force-field adaptation. First of all, the significant effect of *phase* reveals a difference of the intercept of the learning curve between Adapt 1 and Adapt 2. Inspection of the marginal means confirms that this is due to a reduction in intercept during re-adaptation, showing that the adaptation curve of LD of Adapt 2 is significantly shifted downwards compared to Adapt 1. A significant effect is also found for the polynomial function that uses the continuous variable *block*. This effect shows that adaptation occurred; a non-significant effect would imply that no learning took place. Note however that this effect is found for Adapt 1 and 2 combined. The interaction can tell us more about the effect on each phase separately. The interaction was significant so suggests a change of the shape of the learning curve from Adapt 1 to Adapt 2. Therefore, the interaction is followed by Bonferroni-adjusted post-hoc analysis on the marginal means, which shows that the linear term (i.e. slope) significantly different was between Adapt 1 and Adapt 2; $t(12.7) = -2.581$, $p = 0.046$, but not the quadratic term (i.e. curvature); $t(12.9) = 0.811$, $p = 0.864$, meaning that the slope had changed between Adapt 1 and 2 but not the curvature.

2.7 Conclusion

In this Chapter was shown that using a statistical design that allows the addition of relevant random effects can improve the reliability of your statistical tests. Using pilot data we then showed that adaptation and savings on a force-field adaptation task can be determined using a well-designed LME model that includes a 2-degree polynomial function describing the adaptation and a random effect that allows subject-specific variation of the intercept and curve. Similar statistical designs will be used in the coming chapters, but since those studies include several groups an additional fixed effect (*group)* will be included to allow comparison between groups.

Chapter 3

Force-field adaptation reveals altered interference in Parkinson's Disease

3.1 Introduction

People with PD suffer from degeneration of the DA cells in the SNpc. The depletion of dopamine leads to a variety of symptoms, of which rigidity, bradykinesia, tremor and postural instability are the most noticeable and well known. Dopaminergic innervation of the striatum contributes to maintaining a healthy balance of inhibition and excitation within the BG. The BG is best known for its importance in the control of movement, and the motor deficits seen in people with PD emphasizes this. However, much less is known about the consequences of PD pathology on motor learning and motor memory.

Motor learning and motor memory can be studied using motor adaptation paradigms, such as a VMR (Krakauer et al. 2000) or a force-field task (Shadmehr and Mussa-Ivaldi 1994), during which the participant must learn to compensate for the perturbation in order to make accurate movements. Having initially learnt the perturbation, if exposed to the same perturbation for a second time, participants can show improved learning compared to the initial exposure, i.e. savings (Brashers-Krug, Shadmehr, and Bizzi 1996; Krakauer, Ghez, and Ghilardi 2005). On the contrary, performance degrades when participants have to adapt to an opposite or incompatible perturbation, which is thought to occur due to anterograde interference of the first learned perturbation with the second (Brashers-Krug, Shadmehr, and Bizzi 1996; Shadmehr and Holcomb 1999; Shadmehr and Brashers-Krug 1997; Miall, Jenkinson, and Kulkarni 2004). Both the presence of savings and interference indicate that the first learned adaptation is actively held and consolidated to form a motor memory.

Motor adaptation has previously been studied in PD using prism adaptation (Stern et al. 1988; Fernandez-Ruiz et al. 2003; Gutierrez-Garralda et al. 2013) and visuomotor adaptation (Contreras-Vidal and Buch 2003; Marinelli et al. 2009; Bédard and Sanes 2011; Isaias et al. 2011; Leow, Loftus, and Hammond 2012; Leow et al. 2013). The majority of these studies show normal adaptation in PD except for the study by Contreras-Vidal & Buch (2003) who found incomplete error reduction at the end of adaptation. The studies that found normal adaptation and tested for aftereffects showed conflicting results, as some revealed no difference in aftereffects between the PD and Control group (Gutierrez-Garralda et al. 2013; Leow et al. 2012), whilst others showed a difference in aftereffects (Stern et al. 1988; Fernandez-Ruiz et al. 2003). Three studies that tested for savings found a reduction of savings in PD (Marinelli et al. 2009; Bédard and Sanes 2011; Leow, Loftus, and Hammond 2012). One study also found a reduced interference effect (Leow et al. 2013). These studies suggest that PD impacts retention/savings in adaptation more than the mechanisms of adaptation per se.

Kinematic transformations, such as the VMR task used in earlier studies, induce adaptation via a displacement of points or objects in space (Flanagan et al. 1999). However, such adaptation paradigms omit the fact that the mass of the objects that we manipulate influence how we learn to use those objects (Kalaska et al. 1989). During force-field adaptation, the perturbation to normal accurate movements is caused by applying an unexpected force to the movements. A velocity-dependent force-field acting on the arm as it moves through space allows testing of the dynamic component of adaptation that is absent in visuomotor adaptation (Scheidt et al. 2000; Shadmehr and

Mussa-Ivaldi 1994). Several studies suggest that kinematic and dynamic components of motor control have different neural representations in the brain (Crutcher and Alexander 1990; Riehle and Requin 1995) and are influenced differently by lesions of the CNS (Rabe et al. 2009). It has also been suggested that kinematic and dynamic learning use different working memory systems (Krakauer, Ghilardi, and Ghez 1999).

The intention of our study was to investigate savings and interference in PD after adaptation to a dynamic force-field. People with PD and healthy age-matched controls adapted to a clockwise force-field. After a 1-hour break participants were either re-exposed to the same force-field or required to adapt to an opposite (counter clockwise) force-field. Savings and interference were obtained by comparing the initial and secondary adaptation. If motor memory in PD is held less robustly than that in Controls less savings and diminished interference would be expected. To investigate if an extended overnight break revealed any differences in savings and interference the experiment was repeated with a 24-hour break instead of a 1-hour break.

3.2 Materials and methods

3.2.1 Participants

3.2.1.1 Experiment 1 (1-hour break)

Twenty-four people with PD and 24 healthy age-matched controls took part in experiment 1. Participants were randomly allocated to either the savings or interference condition. The savings-condition contained 12 PDs (aged 67 ± 2 (60 - 77), 5 females, 4 left-handed) and 12 Controls (aged 70 ± 2 (58 - 79), 5 females, 1 left-handed). The PD group had a disease duration of approximately 7 ± 1 years. They were tested on the Unified Parkinson's Disease Rating Scale Part III (Motor Examination) on which they scored 48 ± 4. The interference-condition comprised of 12 participants with PD (aged 65 ± 1 (58 - 76), 3 females, 2 left-handed) and 12 Controls (aged 67 ± 2 (59 - 80), 7 females, all right handed). Disease duration was 5 ± 1 years and UPRDS-III 40 ± 3.

3.2.1.2 Experiment 2 (24-hour break)

Twenty-three people with PD and 24 healthy age-matched controls were included in experiment 2. The savings-condition contained 11 PD participants (aged 68 ± 2 (57 – 80), 4 females, 2 left-handed and 1 ambidextrous) and 12 Controls (70 ± 2 (58 – 79), 4 females, 1 left-handed). UPDRS- III score was 44 ± 3 and disease duration 5 ± 1 years. Twelve people with PD (aged 68 ± 2 (57 – 79), 4 females, 1 left-handed) and 12 Controls (70 ± 2 (56 – 78), 2 females, all right-handed) were included in the interference-condition. The PD group had a disease duration of 7 ± 2 years and scored 51 ± 5 on the UPDRS-III.

The 8 subgroups were tested for significant differences of age, gender and handedness, but no differences were found; age: $F(7, 87) = 0.858$, $p = 0.543$; gender: $\chi^2(df = 7, N = 95) = 5.597$, $p = 0.588$, and handedness: $\chi^2(df = 14, N = 95) = 17.725$, $p = 0.220$. In addition, no significant differences were shown for disease duration ($F(3,43) = 0.292$, $p = 0.831$) and UPDRS ($F(3,43) = 1.579$, $p = 0.208$) between the 4 PD subgroups. PD participants remained ON their normal medication, both in experiment 1 and 2, which included various regimes of dopamine receptor agonists, levodopa, and MAO-B inhibitors, see Appendix II for details about medication. All participants gave their written informed consent to take part in the study, and all experimental procedures were approved by the University of Birmingham's Ethical Review Committee and conformed to the Declaration of Helsinki.

3.2.2 Experimental set-up

Participants learned to reach through a velocity-dependent force field applied by a velocity-dependent force-field robot (vBot). The vBOT is a 2D planar manipulandum comprising a two-link carbon fibre arm arrangement, which is driven by motors [for full detail of the apparatus, see (Howard, Ingram, and Wolpert 2009)]. Participants sat in front of the robot, as shown in figure 3.1A, and held the handle of the robotic arm. A small round cursor indicated the handle's position and was projected from a LCD screen onto a semi-silvered mirror horizontally overlaying their plane of movement. Participants were required to move toward themselves from the starting point located in the midline of the screen to a single target 10 cm more proximal. Before the start of a trial, both the starting

point and target were displayed in grey. The starting point turned blue as soon as the cursor entered it to indicate that the participant could start their movement. When the cursor correctly landed in the target, the target turned yellow (HIT), failure to hit the target was indicated by the target turning red (MISS). Both the HIT and MISS were accompanied by a visual 'firework explosion', see figure 3.1C, with the radius of the explosion corresponding to the accuracy of the end point. The starting point correspondingly changed to yellow or red at the end of each trial after which it turned back to grey. The target, however, stayed either yellow or red until the participant had returned to the starting point. After trial completion, the handle was robotically guided back to the starting position.

Participants performed 70 trials of baseline (null field, no force applied) followed by 140 trials of adaptation (clockwise force-field). The strength of the force-field was 12 N/m/s. A break followed, which was 1-hour for participants in experiment 1 and 24-hours for those in experiment 2. After the break participants performed 80 trials of washout (null field), which was followed by another 140 trials of adaptation. Participants in the savings-condition were re-exposed to the clockwise (CW) force-field, while participants in the interference-condition were exposed to a counter-clockwise (CCW) force-field.

Error-clamp trials were pseudo-randomly interspersed among the normal trials with an average of 1 error-clamp per 7 trials. In addition, to capture the retention of force adaptation, the first 10 trials of the washout phase were error-clamp trials. Error-clamp trials were used to measure the compensatory forces produced by the participant see figure 3.1B. During an error-clamp trial lateral errors were clamped at zero (spring

constant = 5000 N/m) and the vBot recorded the lateral forces that the participant produced against the walls of the error-clamp trial. During an error-clamp trial no cursor was seen by the participant, instead hand distance from the starting point was indicated with an expanding semi-circle to remove any information of the direction of the hand.

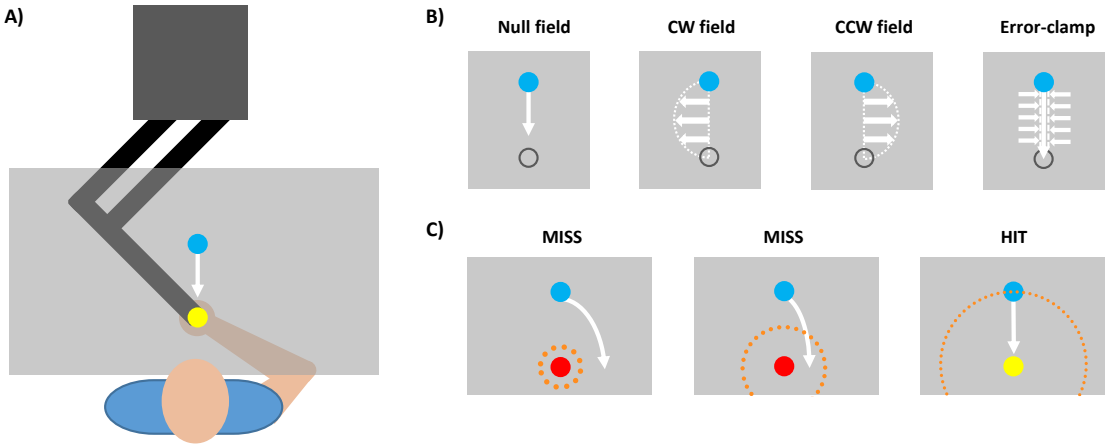


Figure 3.1 Experimental set-up and task details. A) The participant holds the handle of the velocity-dependent force-field robot (vBot) and makes reaching movements from the starting point (blue) to the target (yellow). B) The forces of the vBot are turned off during the baseline and washout phase (Null field). All participants are exposed to a CW force-field during the first adaptation, and during the second adaptation for those in the savings-condition. Participants tested on interference are exposed to a CCW force-field during the second adaptation. Error-clamp trials are interspersed among the null and force-field trials and placed at the beginning of the washout phase. C) Targets that are missed are indicated with a red target, trial hits with a yellow target. In addition, a visual explosion is shown with its radius related to the cursors end-of-trial distance to the target.

3.2.3 Data Analysis

Data recorded by the vBot was transferred to MATLAB (The MathWorks, Version R2016b) for data analysis. For null and force-field trials, lateral deviation (LD) at peak velocity was used as a measure of error, which was calculated by obtaining the position (x-pos) of the cursor when the velocity (y-vel) reached its peak. Outliers (values outside the mean ± 2 * standard deviation (SD)) were removed across subjects after which LD

was averaged in blocks of 5 trials. For every error-clamp trial a force compensation ratio (FC) was calculated according to (similar to Howard et al., 2013):

$$\frac{\int_{t_0}^{t_{end}} actual\ Force}{\int_{t_0}^{t_{end}} ideal\ Force} \times 100\% \qquad \text{[eq. 3.1]}$$

The actual force, i.e. the force produced against the walls of the channel, was divided by the ideal force (i.e. the force required to fully compensate for the applied force-field), defined as a percentage. The ideal force was calculated by multiplication of the actual velocity (y-vel) with the field constant (12 N/m/s). The actual force and ideal force were integrated from t_0 till $t_{end;}$ t_0 indicating the time point that the velocity went above 4 cm/s, t_{end} when it dropped below 4 cm/s. Outliers were again identified and removed if their values were outside ± 2 SD of the mean.

3.2.4 Statistical Analysis

Group differences in initial adaptation (Adapt 1) were tested for statistical significance using a linear mixed effects (LME) model in RStudio (R Core Team 2016). Because participants were all exposed to a clockwise force-field during initial adaptation, the LD and FC of Adapt 1 were collapsed across both conditions (saving and interference), for each group and experiment separately. The LD data was fitted with an LME model using the lme4 package (Bates et al. 2015) with *group* (PD vs Control) and a two degree polynomial function using *block* (blocks 15 [start of Adapt 1] – 42 [end of Adapt 1]) as

fixed effects. The model also included a random effect that allowed the polynomial function to change per subject.

$$LD \sim group \times polynomial(block, 2) + (polynomial(block, 2) \mid subject) \quad \text{[eq. 3.2]}$$

The model was fitted to the data using the Maximum Likelihood method with an R^2 calculated to ascertain how well the model explained the data. F-tests were performed on the fixed effects to assess main effects and interactions. A similar model was fitted to the FC data and tested for significance, but *error-clamp trial* (trials 11 – 31) was used as fixed effect instead of *block*. Note that main effects on the polynomial function or including it are referred to as *block* for the LD data and *trial* for the FC data. Prior to model inference, a *t*-test was performed on the end of baseline for LD (average block 13 – 14) and for FC (average trial 9-10) to ensure that baseline performance was comparable between models.

After the break (Exp1: 1-hour, Exp2: 24-hours) participants performed 80 trials with no extraneous forces applied. These washout trials allowed to measure the retention of the adapted state and reverted the participants to baseline performance before the second adaptation phase. The first 10 trials of this washout phase were error-clamp trials. To see if there was a difference in retention between the PD and Control group the force compensation measured during these error-clamp trials was tested for significance using the LME model. From 38% of all participants (Exp 1: 8 PDs and 10 Controls; Exp 2: 7 PDs and 11 Controls) data from the first error-clamp trial of the washout phase (trial 32) was unsuccessfully collected, therefore for all participants this error-clamp trial was

excluded from any further analysis. LD (block 45 – 58) was similarly tested for group differences.

To explore differences in adaptation following the different interventions (savings and interference) initial adaptation (Adapt 1) was compared to the post-break adaptation (Adapt 2). Similar to the analysis of initial adaptation, a LME model was generated for the LD and FC data of Adapt 1 (blocks 15 – 42 / error-clamp trials 11 – 31) and Adapt 2 (blocks 59 – 86 / error-clamp trials 52 – 72) for experiment 1 and 2 separately. The LME model was similar to the one described above (eq. 3.2), but *phase* (Adapt 1 vs Adapt 2) was added both as a fixed and random effect, allowing group inference while simultaneously permitting the polynomial function to change for each subject and phase. Equation 3.3 shows the LME model for the LD data.

$$LD \sim group \times phase \times polynomial(block, 2) + (phase \times polynomial(block, 2) \mid subject) \quad \text{[eq. 3.3]}$$

The LD and FC data were tested for main effects and interactions using F-tests. Subsequently, significant interaction effects were followed by Bonferroni adjusted post-hoc analysis using the marginal means. Before differences between Adapt 1 and Adapt 2 were tested, a separate validation model was used to test for differences in baseline and washout. For every condition, the last two LD blocks and the last two FC error-clamp trials of baseline and washout were averaged and tested for the same main effects and interactions as above.

3.3 Results

3.3.1 Experiment 1

Participants performed the protocol as described in the method section. Figure S1 and S2 (Appendix I) show some typical data of PD and Control subjects for the savings and interference condition of experiment 1. Participants showed a large deflection when the force-field was introduced as seen during early A1 and A2, while deflection was lower during baseline and washout. The averaged LD and FC are shown in figure 3.2 and 3.3.

The results from experiment 1 showed that people with PD display similar adaptation to a CW force-field as Controls. When the force-field was removed retention and de-adaptation after 1-hour were also comparable between the groups. Controls showed a strong effect of interference both for LD and FC. Interestingly, interference was nearly absent in the PD group. Savings of LD were present and similar between groups, but the FC data did not reveal any significant savings.

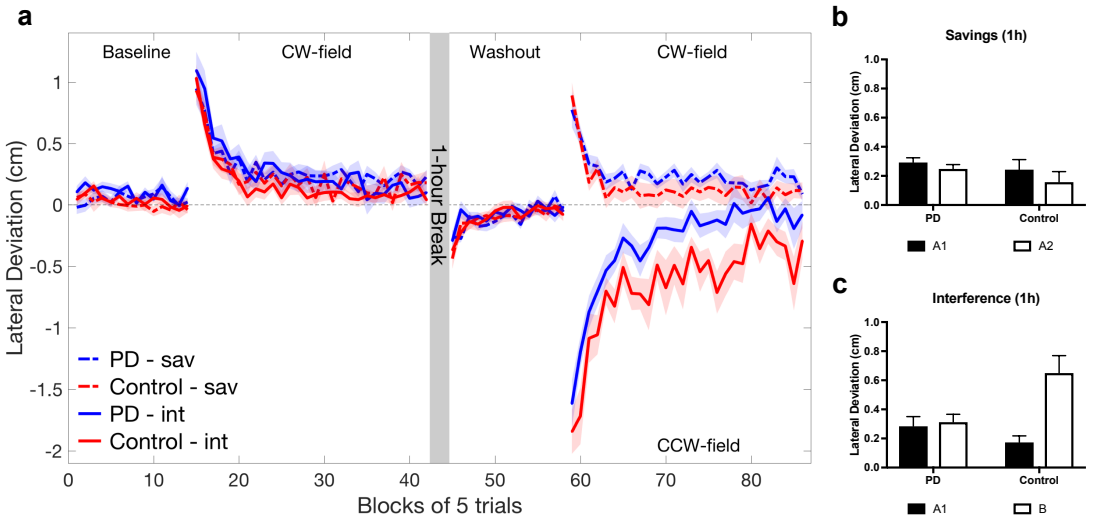


Figure 3.2 Lateral deviation - Experiment 1. a) LD during Baseline, Adapt 1, Washout, and Adapt 2 for the PD (blue) and Control (red) group both for the savings-condition (dotted lines) and interference-condition (solid line). b) The average LD of Adapt 1 (A1 – CW field – block 15 - 42) and Adapt 2 (A2 – CW field – block 59 - 86) displayed for both groups in the savings condition. c) Average LD of Adapt 1 (A1 – CW field) and Adapt 2 (B – CCW field) of the PD and Control group in the interference condition.

Figure 3.3 Force compensation - Experiment 1. a) FC during Baseline, Adapt 1, Washout, and Adapt 2 for the PD (blue) and Control (red) group both for the savings-condition (dotted lines) and interference-condition (solid line). b) The average FC of Adapt 1 (A1 – CW field – EC trial 11 - 31) and Adapt 2 (A2 – CW field – EC trial 52 - 72) displayed for both groups in the savings condition. c) Average FC of Adapt 1 (A1 – CW field) and Adapt 2 (B – CCW field) of the PD and Control group in the interference condition.

3.3.1.1 Initial adaptation was similar between the PD and Control group

Initially, all participants were exposed to the CW force-field before being tested on the same force-field (savings-condition) or a CCW force-field (interference-condition). Therefore, the lateral deviation and force compensation of Adapt 1 for the PD and Control groups were collapsed across the two conditions to look at differences in initial adaptation between PD (N = 24) and Controls (N = 24). No significant differences in baseline were observed for either metric (LD: $t(46) = 1.368$, $p = 0.178$; FC: $t(46) = -1.836$, $p = 0.073$. When the force-field was introduced both groups showed a deviation of approximately 1cm (block 15); PD 1.0 cm ± 0.1, and Controls 1.0 cm ± 0.1. At the end of adaptation (block 42) error was reduced to 0.2 cm ± 0.1 for PDs and 0.1 cm ± 0.1 for Controls. Linear mixed-effects modelling of the LD data ($R^2 = 0.648$) showed a main effect of the polynomial including the continuous variable *block,* $F(2, 47.41) = 75.627$, $p < 0.001$, but no main effect of *group*, $F(1, 47.92) = 2.685$, $p = 0.108$, or *group* × *block* interaction, $F(2, 47.41) = 0.801$, $p = 0.455$, indicating that adaptation occurred in both groups in a similar way. FC at the end of adaptation (trial 31) was 78.6 ± 3.5% for PDs and 83.6 ± 2.2% for Controls. The FC data was also fitted with an LME model ($R^2 = 0.512$) and showed similar results; *group*: $F(1, 46.83) = 1.736$, $p = 0.194$, *trial*: $F(2, 66.16) = 208.423$, $p < 0.001$, and *group* × *trial*: $F(2, 66.16) = 0.465$, $p = 0.631$. These results suggest that people with PD adapt to a clockwise force-field in a similar way as healthy age-matched Controls.

3.3.1.2 Both groups de-adapted during washout

Following the initial adaptation participants had a 1-hour break after which a period of washout began. During washout conditions were the same as during baseline, i.e. no forces were applied, and allowed to measure retention of the adapted state and de-adaptation. The PD and Control group had retained an FC (error-clamp trial 33) of 27.5 ± 7.5 % and 31.9 ± 5.1 % respectively, which was Δ 36.8 ± 10.9 % for people with PD and Δ 41.0 ± 6.3 % for Controls compared to their FC at the end of Adapt 1. In the following error-clamp trials the FC reduced further (LME fit $R^2 = 0.815$) as *trial* was significant; $F(2,44.77) = 8.927$, $p < 0.001$, but this reduction was not different between groups; *group:* $F(1, 44.19) = 0.002$, $p = 0.968$, and *group* × *trial*: $F(2, 44.77) = 0.735$, $p = 0.485$. Participants also showed a negative deviation at the start of the washout period as shown by LD; PD: -0.3 ± 0.0 cm, and Controls: -0.4 ± 0.0 cm (Block 45), indicating some retention. Statistical tests of LD (LME $R^2 = 0.492$) showed no group differences for Block 45 – 58; *group:* $F(1, 48.00) = 0.147$, $p = 0.703$; and *group* × *block*: $F(2, 47.46) = 1.443$, $p = 0.246$, but similar to the FC there was significant de-adaptation in both groups; *block*: $F(2, 47.46) = 48.964$, $p < 0.001$.

3.3.1.3 Baseline and washout performance was comparable (but not identical) between groups

After the washout phase participants performed either the same CW force-field (savings-condition) or an opposite – CCW – force-field (interference-condition). To ensure similar motor performance at the end of baseline and the end of washout comparisons were made

between the groups using a mixed model on the LD and FC data. For the savings-condition (LD: $R^2 = 0.043$; FC: $R^2 = 0.131$) no main effect of *group* (LD: F(1, 23.99) = 0.514, p = 0.481; FC: F(1, 24) = 0.958, p = 0.338), *phase* (*baseline vs. washout*; LD: F(1, 23.99) = 0.058, p = 0.812; FC: F(1, 24) = 0.041, p = 0.842), nor an interaction effect of *group* × *phase* (LD: F(1, 23.99) = 0.048, p = 0.828; FC: F(1,24) = 0.591, p = 0.450) was found.

For the interference condition (LD: $R^2 = 0.246$; FC: $R^2 = 0.687$) no main effect of *group* was found (LD: F(1, 24.00) = 1.391, p = 0.250; FC: F(1, 24.28) = 1.040, p = 0.318), but there appeared to be an overall difference between the end of baseline and end of washout as *phase* was significant for LD; F(1, 24.00) = 4.246, p = 0.050; and FC; F(1, 23.64) = 11.131, p = 0.003. A significant *group* × *phase* interaction was also shown for FC (F(1, 23.64) = 6.637, p = 0.017), but not LD (F(1, 24.00) = 1.756, p = 0.198). Bonferroni adjusted post-hoc analysis revealed that the FC of baseline and washout differed in PDs; t(25.19) = -4.070, p = 0.002, but not Controls; t(25.85) = -0.504, p = 1.000. More importantly, no direct group differences between the PD and Control group were found for baseline (t(38.19) = -1.937, p = 0.240) and washout (t(37.07) = 0.197, p = 1.000).

3.3.1.4 Both groups displayed savings of LD

To get a better understanding of the within group changes, the LD and FC of Adapt 1 and Adapt 2 were replotted for each group separately in figure 3.4. F-tests on the LME of LD ($R^2 = 0.605$) of the savings condition revealed a significant effect of *phase*, F(1, 23.93) =

10.382, p = 0.004, but no main effect of *group*, F(1, 23.98) = 0.964, p = 0.336, or *group* × *phase* interaction F(1, 23.93) = 1.162, p = 0.292, suggesting that there was a similar improvement during Adapt 2 in both groups. For FC (R^2 = 0.461), no main effect of *group* (F(1, 23.77) = 0.099, p = 0.756), and *phase*; F(1, 24.11) = 3.090, p = 0.091, was found, nor a *group* × *phase* interaction, F(1, 24.11) = 3.096, p = 0.091. However, both *phase* and *group* × *phase* showed a trend and together with figure 3.4 (c+d) it seems plausible that some savings were present, more so in Controls. Altogether, savings of LD were present and similar between the PD and Control group, but the FC data did not reveal any significant savings in both groups.

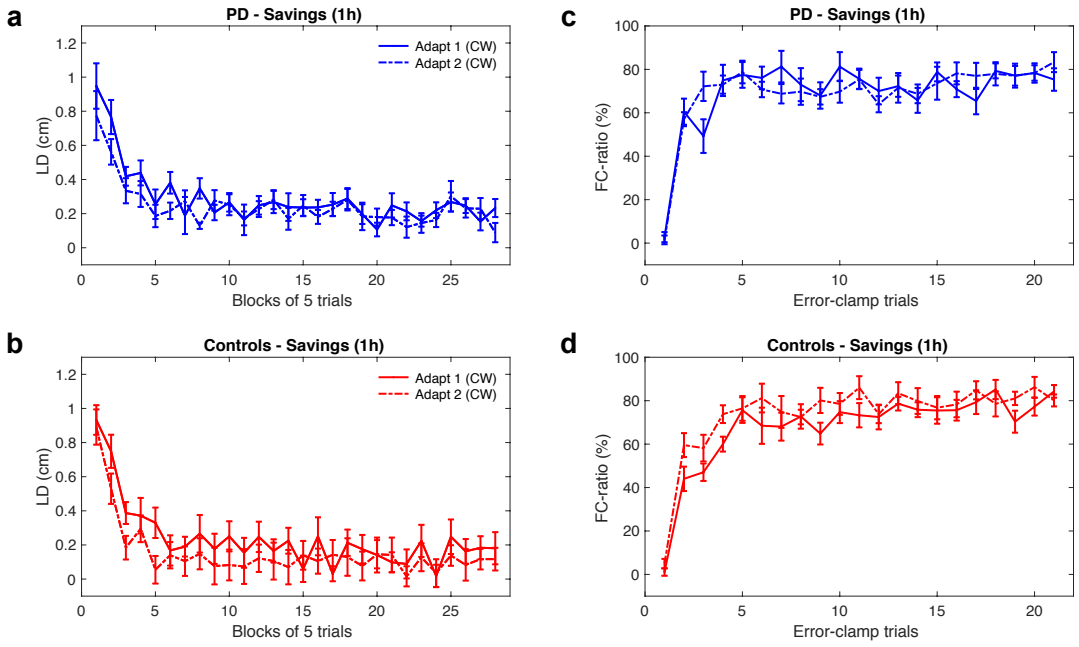


Figure 3.4 Experiment 1 (1-hour break) - LD (a-b) and FC data (c -d) of Adapt 1 (solid lines) and Adapt 2 (dotted lines) displayed separately for the PD (a – c) and Control group (b – d) from the savings-condition.

3.3.1.5 Interference was nearly absent in the PD group

Results of the interference-condition showed that the performance of an opposite force-field had a detrimental effect on the LD and FC in Controls, but not in people with PD. The LD data (R^2 = 0.733) revealed a main effect of *phase*, F(1, 24.00) = 12.422, p = 0.002, and a *group* × *phase* interaction effect, F(1, 24.00) = 10.569, p = 0.003, but no main effect of *group* (F(1, 24.00) = 1.936, p = 0.177). Bonferroni adjusted post-hoc analysis on the interaction effect revealed a significant increase of LD during Adapt 2 in Controls; t(26.08) = -3.973, p = 0.002, but not PDs; t(26.08) = 0.703, p = 1.000, indicating that the intercept had changed from Adapt 1 to Adapt 2 only in Controls. An overall interaction of phase × block was also found; F(2, 29.28) = 6.175, p = 0.006, but no group × phase × block interaction; F(2, 29.28) = 1.743, p = 0.193, suggesting that in both groups the slope/curvature of adaptation had undergone some changes. In figure 3.5 can be seen that while the PD group only shows an increased LD early during Adapt 2, Controls maintain a higher LD throughout.

The FC data (R^2 = 0.575) also showed a main effect of *phase* (F(1, 23.89) = 9.105, p = 0.006) and a *group* × *phase* interaction (F(1, 23.89) = 5.654, p = 0.026), but no effect for *group* (F(1, 23.89) = 0.186, p = 0.670). Closer inspection of the *group* × *phase* interaction effect showed again that the interaction was caused by a worsening of performance, i.e. significant reduction of FC, during Adapt 2 in Controls (t(26.06) = 3.841, p = 0.003), but not in PDs (t(26.02) = -0.158, p = 1.000). In addition a *group* × *phase* × t*rial* effect was found for FC; F(2, 33.17) = 3.894, p = 0.030, suggesting that not only the intercept but also the shape of the adaptation curve of FC differed between

groups. Post-hoc tests revealed that for Adapt 2 the quadratic term of the polynomial function, i.e. the curvature, was altered between the PD and Control group; t(24.15) = -2.729, p = 0.023, but not the linear term (i.e. the slope); t(25.88) = 0.522, p = 1.000. These results show that FC was subject to interference in Controls, but not in people with PD.

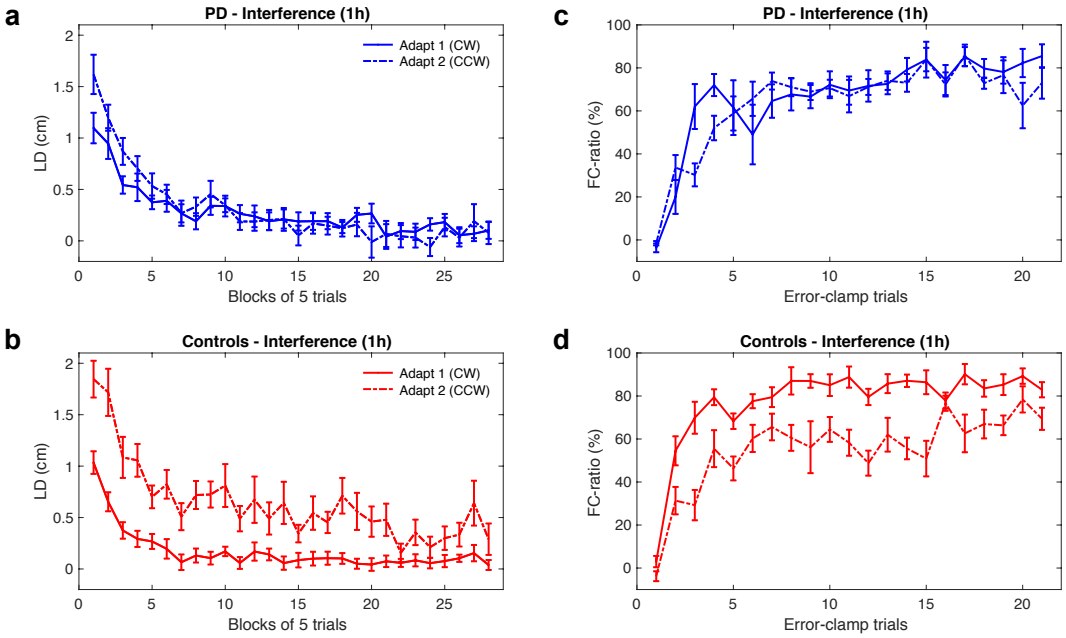


Figure 3.5 Experiment 1 (1-hour break) - LD (a-b) and FC data (c -d) of Adapt 1 (solid lines) and Adapt 2 (dotted lines) displayed separately for the PD (a – c) and Control group (b – d) from the interference-condition.

3.3.2 Experiment 2

Participants in experiment 2 performed the second adaptation after 24-hours instead of 1-hour, to see if an extended overnight break revealed any differences in savings and interference. The averaged LD and FC are shown in figure 3.6 and 3.7. Retention and savings were similar between the Control and PD group. Also, interference was present in both groups, but seemed reduced in PD. However, in contrast to experiment 1, the PD group displayed incomplete error reduction at the end of adaptation.

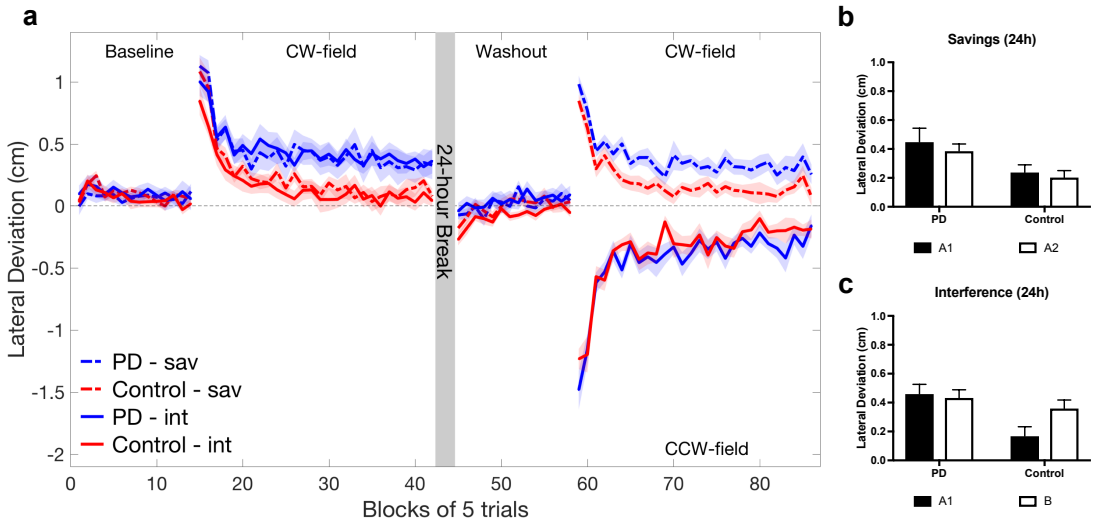


Figure 3.6 LD - Experiment 2 (24-hour break) a) LD during all phases (Baseline, Adapt 1, Washout, Adapt 2) shown for the savings condition (dotted lines) and interference condition (solid lines) for the PD (blue) and Control (red) group. b) Average LD for the PD and Control group of the savings condition during Adapt 1 (A1 – CW field) and Adapt 2 (A2 – CW field). c) Average LD of A1 and B (Adapt 2 - CCW field) for both groups of the interference condition.

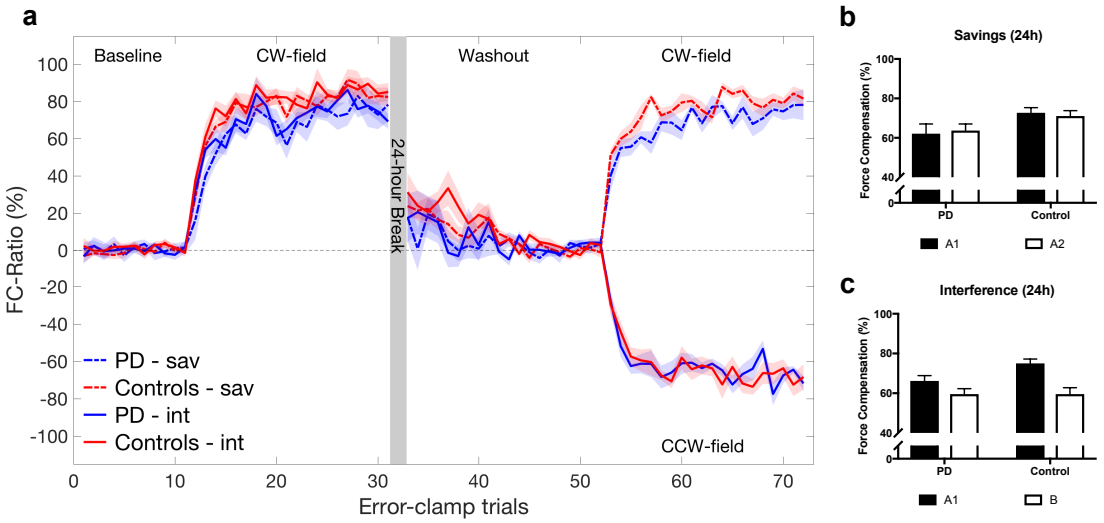


Figure 3.7 FC - Experiment 2 (24-hour break). a) FC during all phases (Baseline, Adapt 1, Washout, Adapt 2) shown for the savings (dotted lines) and interference condition (solid lines) for the PD (blue) and Control (red) group. b) The average LD of the PD and Control group in the savings condition displayed for Adapt 1 (A1) and Adapt 2 (A2). c) Average LD of A1 and B (Adapt 2 – CCW field) for the PD and Control group of the interference condition.

3.3.2.1 Error reduction was lower in the PD group

Similarly to experiment 1 the initial adaptation was collapsed across conditions and tested for group differences. The end of baseline was not significantly different between the PD (N = 23) and Control group (N = 24); LD: $t(35.39) = 0.847$, $p = 0.403$, and FC: $t(45) = -1.273$, $p = 0.210$. When the force-field was introduced the PD and Control group had a deviation of 1.1 ± 0.1 cm and 0.9 ± 0.1 cm, respectively, a similar deviation to experiment 1. Controls adapted well to the force-field. Their deviation at the end of adaptation (block 42) was 0.1 ± 0.0 cm and the FC was increased to 85.2 ± 3.1% (error-clamp trial 31). Surprisingly, the PD group in experiment 2 did not adapt as well as those in Experiment 1, see figure 3.6. They initially showed rapid adaptation to the force-field but maintained a deviation of 0.3 ± 0.1 cm at the end of adaptation. The force compensation of the PD

group was increased to 75.5 ± 3.9 %, which was slightly lower but comparable to the FC of the PD group from experiment 1. F-tests confirmed group differences for LD (R^2 = 0.736) as a main effect of *group*, F(1, 46.98) = 13.888, p < 0.001, and an interaction effect of *group* × *block*, F(2, 74.37) = 5.388, p = 0.007, were found. A post-hoc test revealed that the quadratic term (i.e. curvature) ; t(48.21) = -3.222, p = 0.005, but not the linear term (i.e. slope); t(49.04) = 1.419, p = 0.324, of the LD learning curve significant was between the groups. Altogether, these results indicate group differences in intercept and curvature, but not the slope, of LD reduction. A main effect of *block* was also found, F(2, 74.37) = 119.220, p < 0.001. Statistical tests on the FC data (R^2 = 0.559) also revealed a main effect of *group*, F(1, 45.71) = 9.706, p = 0.003, and *trial*, F(2, 85.28) = 382.160, p < 0.001, but not an interaction effect of *group* × *trial*, F(2, 85.28) = 0.671, p = 0.514, indicating that only the intercept but not the shape of the learning curve differed between groups.

3.3.2.2 Retention after 24-hours was similar between the groups

Retention of the FC was lower in both groups compared to experiment 1; PD: 17.6 ± 8.9 % and Controls: 21.9 ± 4.8 % (error-clamp trial 33), which was Δ 28.1 ± 12.5 % and Δ 27.5 ± 5.6 % compared to the end of Adapt 1, respectively. So in both groups roughly 28 % of FC was retained after 24-hours. Opposed to experiment 1, no significant de-adaptation was found for FC across groups (LME R^2 = 0.818) as *trial* was not significant; F(2, 44.57) = 1.634, p = 0.207. In addition no *group*; F(1, 45.72) = 2.356, p = 0.132, or *group* × *trial* ; F(2, 44.57) = 0.063, p = 0.939, differences were found, suggesting that

retention of the adaption was substantially reduced compared to the 1-hour break and similar in both groups. The LD after 24-hours (block 45) was -0.1 ± 0.0 cm for people with PD and -0.2 ± 0.0 cm for Controls. Analysis of LD (R^2 = 0.607, block 45 - 58) did show significant reduction of LD in both groups 24-hours after exposure to the force-field; *block*: F(2, 83.39) = 22.918, p < 0.001. A significant effect of *group* was also found; F(1, 47.00) = 4.113, p = 0.048, indicating a change in intercept between the PD and Control group. This difference of intercept is presumable due to the offset between groups at the end of adaptation. No *group* × *block* effect was observed; F(2, 83.39) = 0.843, p = 0.434. Together with earlier findings these results suggest that no differences in retention took place between people with PD and Controls. In addition, these results show that retention of force compensation larger is after 1-hour than 24-hours.

3.3.2.3 Baseline and washout performance was comparable

Before comparison of Adapt 1 and Adapt 2, the end of baseline and end of washout were explored. For the savings condition (LD: R^2 = 0.561; FC: R^2 = 0.533) no main effect of *group* (F(1, 23.00) = 0.126, p = 0.726), or *phase* (*baseline vs. washout;* F(1, 23.00) = 0.314, p = 0.581), nor an interaction effect of *group* × *phase* (F(1, 23.00) = 0.514, p = 0.481), was found for LD, nor for FC; *group*: F(1, 22.99) = 0.001, p = 0.982, *phase*: F(1, 23.00) = 0.011, p= 0.919 and *group* × *phase*: F(1, 23.00) = 0.402, p = 0.532.

For the interference condition (LD: R^2 = 0.713; FC: R^2 = 0.219), *group* (F(1, 24.00) = 1.613, p = 0.216), *phase* (F(1, 24.00) = 0.384, p = 0.541), and *group* × *phase* (F(1, 24.00) = 0.006, p = 0.941), differences were absent for LD and no main effect of

group (F(1, 24.28) = 0.076, p = 0.786) and *phase* (F(1, 24.17) = 2.243, p = 0.147) was shown for FC. There was an effect of *group* × *phase* for FC; F(1, 24.17) = 4.981, p = 0.035, but Bonferroni adjusted post-hoc analysis did not reveal a significant difference between baseline and washout in PDs; t(26.45) = -2.486, p = 0.078, and Controls; t(25.33) = 0.503, p = 1.000. Also, no group differences were found for Adapt 1, t(50.77) = -1.640, p = 0.429, or Adapt 2, t(50.87) = 1.215, p = 0.920.

3.3.2.4 Both the PD and Control group displayed savings after 24-hours

Similar to the results discussed above the PD group in the savings-condition showed incomplete LD reduction at the end of Adapt 1 (block 42); 0.3 ± 0.1 cm, and Adapt 2 (block 86); 0.3 ± 0.1 cm, while Controls had an error of 0.1 ± 0.1 cm (Adapt 1 and Adapt 2). Statistical tests on the LD (R^2 = 0.697) of the adaptation phases revealed a main effect of *group*; F(1, 23.00) = 5.869, p = 0.024, confirming the bias between the groups across both phases. No interaction effect of *group* × *phase* (F(1, 23.00) = 0.205, p = 0.655) was found, indicating that phase related group differences in LD reduction were absent. In addition, *phase* was not significant; F(1, 23.00) = 2.568, p = 0.123, but *phase* × *block* was; F(2, 45.00) = 7.126, p = 0.002. Further analysis revealed that the slope, t(22.14) = -3.442, p = 0.005, but not the curvature, t(24.33) = 1.425, p = 0.334, significantly different was between Adapt 1 and 2 in both groups. This is opposed to experiment 1 where the intercept, but not the shape of the adaptation curve changed.

F-tests on the FC model (LME R^2 = 0.564) revealed the same results as for LD; *group*: F(1, 22.14) = 5.076, p = 0.035, *group* × *phase*: F(1, 22.70) = 0.533, p = 0.473,

phase: F(1, 22.70) = 0.070, p = 0.793, and *phase* × *trial*: F(2, 170.41) = 4.252, p = 0.016. Post-hoc tests on the latter interaction showed again that the slope, t(21.29) = 2.603, p = 0.033, was altered during the second adaptation. The curvature of the learning curve was not different; t(21.60) = -1.277, p = 0.430. Altogether, the results show that the slope of adaptation differed between Adapt 1 and Adapt 2, both for LD and FC, and that this was unaltered between the groups. Inspection of the interaction plots showed that, especially during the initial phase of Adapt 2, LD was lower and FC was higher for both groups compared to their performance during Adapt 1, also see figure 3.8. We conclude that both groups displayed savings after 24 hours.

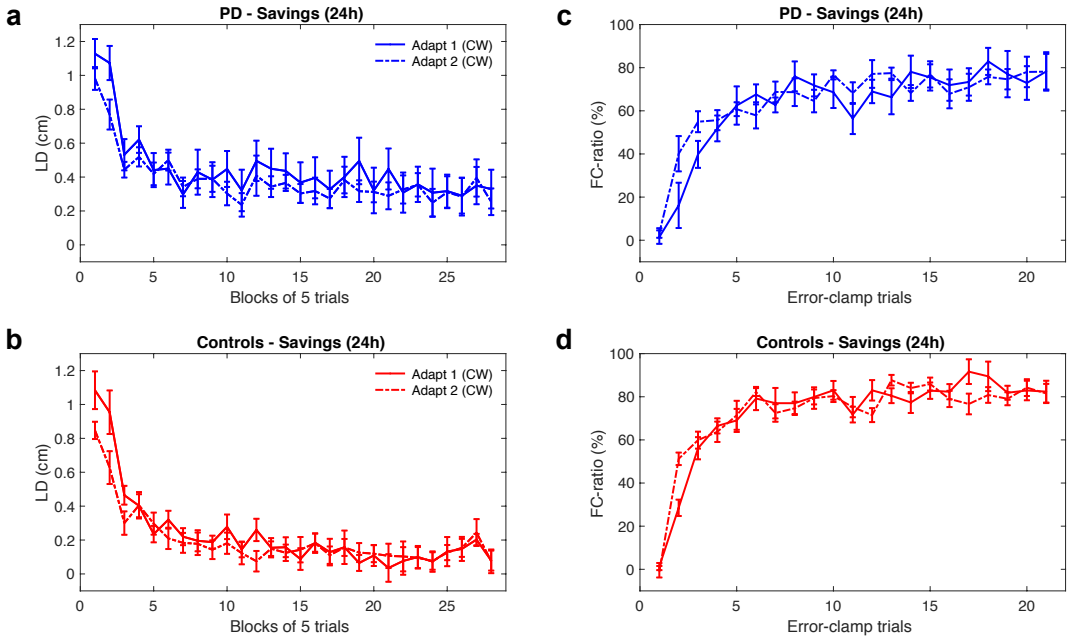


Figure 3.8 Experiment 2 (24-hour break) - LD (a-b) and FC data (c -d) of Adapt 1 (solid lines) and Adapt 2 (dotted lines) displayed separately for the PD (a – c) and Control group (b – d) from the savings-condition.

3.3.2.5 Interference was present in both groups but reduced in PD

Analysis of the interference-condition showed again a main effect of *group* for LD (R^2 = 0.674); F(1, 24.00) = 8.604, p = 0.007, no main effect of *phase*; F(1, 24.00) = 2.061, p = 0.164, and a significant interaction for *phase* × *block*; F(2, 30.74) = 6.817, p = 0.004, which seemed mainly due to differences in the slope, t(26.08) = 3.068, p = 0.010, rather than the curvature of learning, t(24.13) = -2.306, p = 0.060. The *group* × *phase* interaction was not significant, but it did show a trend; F(1, 24.00) = 3.653, p = 0.068. The *group* × *phase* interaction plots showed that for Controls the LD during Adapt 2 was higher throughout all blocks compared to Adapt 1. In the PD group the LD only increased during the first few blocks after which it reduced to values below those of Adapt 1.

For the LME of FC (R^2 = 0.512) a main effect of *phase* was found; F(1, 23.74) = 19.082, p < 0.001, but no effect of *group;* F(1, 23.93) = 2.957, p = 0.098, *group* × *phase;* F(1, 23.74) = 3.228, p = 0.085, and *phase* × *trial*; F(2, 45.77) = 3.113, p = 0.054, although all showed a trend. Similar to the LD, Controls displayed reduced FC throughout Adapt 2 compared to Adapt 1, see figure 3.9. For the PD group, FC was also reduced after the first few trials. Altogether the results show a substantial interference effect in Controls as well as some interference in PD.

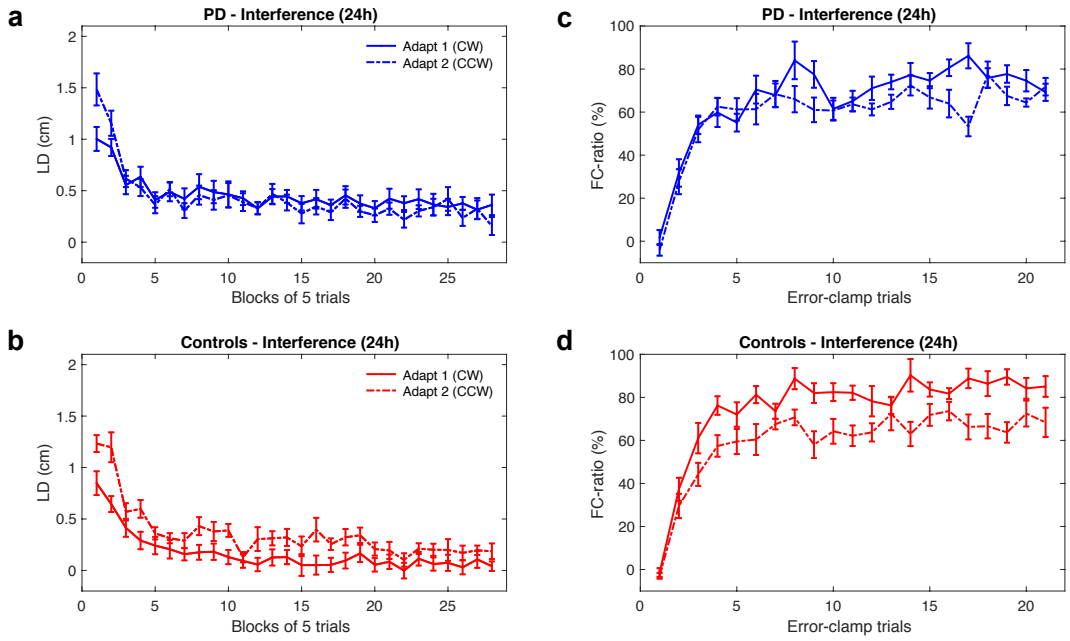


Figure 3.9 Experiment 2 (24-hour break) - LD (a-b) and FC data (c -d) of Adapt 1 (solid lines) and Adapt 2 (dotted lines) displayed separately for the PD (a – c) and Control group (b – d) from the interference-condition.

3.4 Discussion

In this study we tested the hypothesis that people with PD have impaired motor memory following force-field adaptation by investigating whether the phenomena of savings and interference 1-hour and 24-hours after adaptation were altered in PD. Controls displayed a strong effect of interference after 1-hour, as expected, but an interference effect was nearly absent in the PD group. Interference was also seen in Controls 24-hours after initial adaptation, though to a lesser degree, and interference seemed present but smaller in people with PD. No significant differences were found between the PD and Control group of the savings-condition, when they were re-tested on the same force-field 1-hour and 24-hours after adaptation, but an overall enhancement of adaptation was found indicating the presence of savings in both groups. Altogether, people with PD appear to be less susceptible to interference but have relatively intact savings after force-field adaptation compared to Controls. In addition, initial adaptation was similar between the groups of experiment 1, but in experiment 2 the PD group displayed incomplete error reduction. No differences in retention was found between the groups.

Reduced interference in PD seen in our study is in line with the results presented by Krebs et al. (2001), who showed unaltered hand displacement in people with PD following negative transfer (when a force-field switched from the learnt direction to the opposite, with no washout) while hand displacement increased in Controls. Impairment of interference in PD was also shown by a study on kinematic adaptation (Leow et al. 2013), which investigated interference after limited and extended training using a VMR task and found interference in Controls (though only after extended training), but not in

the PD group. The paradigm continued with a washout period and a test for savings, which were present only for Controls both for limited and extended training. Leow and colleagues (2013) argued that interference was caused by use-dependent plasticity (UDP), a process where the continuous repetition of the same movement creates a bias (Diedrichsen et al. 2010), rather than reinforcement mechanisms, a process where correct and incorrect responses are modulated through positive and negative feedback (Huang et al. 2011). This argument was based on the fact that interference was only induced in Controls after extended training (and therefore UDP dependent), while savings were present in both training schemes. If UDP, and not operant reinforcement, is responsible for interference then our results suggest that in people with PD UDP and not operant reinforcement was affected during adaptation to the force-field as only interference and not savings were affected in our PD group. Leow et al.'s interpretation is in contrast to Huang et al. (2011) who claims that operant reinforcement processes underlie both interference and savings after adaptation, it also contradicts earlier research which has shown that operant reinforcement impaired is in PD (Frank, Seeberger, and O'Reilly 2004; Shohamy et al. 2005; Rutledge et al. 2009).

In contrast to our findings, studies on kinematic adaptation have shown that people with PD do not display savings after a visuomotor rotation (Marinelli et al. 2009; Bédard and Sanes 2011; Leow, Loftus, and Hammond 2012). Marinelli et al. (2009) was the first to test for savings in a group of 5 PDs and 5 Controls 48 hours after initial adaptation and showed non-significant savings in PD. The absence of savings in PD became more apparent in their second experiment including six drug-naïve patients where

targets were shown in a predictable counter-clockwise order and savings were tested 24 hours later. The decline in error from their second experiment (first experiment not shown) suggests that asymptote is only just reached at the end of the initial adaptation possibly limiting reinforcement of the adapted state. Our results show that adaptation plateaus early into adaptation, both in Controls and people with PD, leaving many trials left for reinforcing the adapted state, which might have enhanced the formation of savings in PD. However, Bédard & Sanes (2011) investigated if extended training would help recover savings in PD and showed that despite similar initial adaptation rates and prolonged repetition of the learned state no savings were found in the PD group immediately or 24-hours after adaptation. In our study participants adapted to a single target, which is in contrast to the studies above involving adaptation to multiple targets. Reinforcement processes might be compromised in PD due to the simultaneous adaptation to multi-targets. However, Leow et al. (2012) found impaired savings in PD shortly and 24-hours at recall using a single target making this theory unlikely.

Although problems with consolidation of the adapted state, possibly through deficient operant reinforcement mechanisms, could have explained the strong reduction of interference seen in our PD group the presence of largely intact savings makes it unlikely that incomplete consolidation is (solely) underlying the severe deficit in interference seen in our PD groups. Instead, our results could very well represent a problem with the retrieval process of the adapted state. Some studies provide evidence that a motor state is consolidated in relation to relevant contextual cues present during adaptation (Howard, Wolpert, and Franklin 2013; Azadi and Harwood 2014; Caithness

et al. 2004; Nakahara et al. 2004). If contextual cues are indeed also responsible for the activation of a motor memory it would be possible that in fact people with PD do not fail to consolidate the adapted state, but that in some cases this memory is not elicited where in healthy controls it would, such as when exposed to an opposite force-field or during a VMR task. Failure to elicit a motor memory may be tightly linked to overactivity of the inhibitory pathway within the BG caused by PD pathology. Increased inhibition of the BG system could lead to more suppression of the memory of the initial perturbation when performance deteriorates such as during interference; e.g. a weaker link between context and motor state makes them disregard it more easily. This theory would explain why our PD groups only show a decline in performance at the start of the opposite perturbation, where the observation of large errors causes them to disregard the initially adapted state leading to less interference. Re-exposure to the same field, such as when measuring savings, does not require and provoke similar suppression. Whether context-motor associations are less strong in PD and contribute to their motor memory problems has never been directly investigated.

No difference between the PD and Control group were shown for retention after 1-hour or 24-hours. VMR studies also failed to find group differences in after-effects (Leow et al. 2012; Gutierrez-Garralda et al. 2013, and results from Bédard and Sanes (2011) imply similar retention between the groups although no statistics were reported). However, studies using prism adaptation indicated some group dissimilarities. Stern et al. (1988) showed that while both the PD and Control group displayed after-effects, they lasted longer in Controls than in people with PD and Fernandez-Ruiz et al. (2003)

reported a reduced after-effect in the PD group for motor adaptation, which was determined using the first throw after the prisms were removed. In our study, retention in the Control and PD group was similar and seemed larger in the 1-hour than the 24-hour group, which was not surprising since this has been shown by earlier research (Criscimagna-Hemminger and Shadmehr 2008). Savings and interference have also been shown to decline with passage of time (Brashers-Krug, Shadmehr, and Bizzi 1996; Krakauer, Ghez, and Ghilardi 2005; Shadmehr and Brashers-Krug 1997), which is what we observed for interference, but savings as measured with FC were only shown after 24-hours and not after 1-hour. Interestingly, people with PD appeared to show interference after the 24-hour break as group differences were only indicated by a trend and plots showed reduced FC after the first few trials of adaptation. This finding could indicate that passage of time reinstates interference in PD, although the overall reduction of interference in Controls caused by passage of time is presumably contributing to the weak group difference.

One caveat in our study that should be acknowledged is the difference in initial adaptation present in the two PD groups. We found both complete (Exp 1) and incomplete (Exp 2) adaptation in the PD group. This reflects the literature where both normal (Fernandez-Ruiz et al. 2003; Marinelli et al. 2009; Bédard and Sanes 2011; Leow, Loftus, and Hammond 2012; Gutierrez-Garralda et al. 2013; Leow et al. 2013) and decreased adaptation (Krebs et al. 2001; Contreras-Vidal and Buch 2003) have been reported in PD. It should be noted that the only other study using force-field adaptation in PD by Krebs and colleagues (2001) also found incomplete adaptation. In our two experiments PD

groups had worse final levels of adaptation (LD of 0.2 and 0.3 cm in Exp 1 & 2 respectively) compared to Controls (LD of 0.1 cm in both experiments), though only the difference in Experiment 2 proved significant. Also, despite the slight differences seen in final levels, there is still a large reduction of error indicating that adaptation has taken place. These findings, with those already in the literature suggest that adaptation may be affected, but only to a small degree in PD. Moreover, we believe that due to carefully chosen statistical designs an effect of final levels on group differences of savings and interference was eliminated.

Contreras-Vidal & Buch (2003), who found incomplete error reduction by their PD group, exposed participants to a 90º rotation, which was much larger than the 30º that was used by the other VMR studies. Marinelli et al. (2017) suggest that such a large rotation leads to the use of explicit strategies, opposed to the implicit learning that occurs during a 30º rotation, and therefore more cognitive processing, which may be affected in PD (Robbins and Cools 2014). It has also been shown that people with PD display larger errors compared to Controls when the perturbation is explicit opposed to the implicit gradual introduction of a perturbation (Mongeon, Blanchet, and Messier 2013) and that dopaminergic medication can have either positive or negative effects on performance depending on the subject, in line with Cools (2006), who proposed an 'overdose-model'; a model that entails that L-DOPA alleviates DA depleted areas, but simultaneously 'overdoses' brain areas with sufficient DA present. Force-field adaptation involves both implicit and explicit components (Mcdougle, Bond, and Taylor 2015), so it is possible that differences in cognitive decline and dopaminergic treatment between the groups has

led to disparities in the asymptote of adaptation. No noticeable changes in cognition were observed, but in future studies we plan to use cognitive measures to assess cognitive performance.

What we did observe was that the people with PD from experiment 2 mostly reported and displayed symptoms on the left side (17 left-sided/ 3 right sided / 4 both), while those in experiment 1 had a more equal number of people with left and right side affected (10 left-sided/10 right-sided/ 4 both). The BG has shown to display contralateral deterioration in patients with unilateral PD (Heinrichs-Graham et al. 2017), implying that those with left-sided symptoms have right-sided dysfunction of the BG system, which may have affected cerebellar-dependent adaptation of the right limb to a higher extend. Although this is highly speculative, investigating the effect of laterality of PD pathology on motor adaptation and subsequent formed memory might clear up some discrepancies present in the current literature.

In our study all PD participants remained on their normal medication. Could medicated state have affected the results? Most studies on adaptation and motor memory in PD tested participants ON medication (Stern et al. 1988; Fernandez-Ruiz et al. 2003; Bédard and Sanes 2011; L. A. Leow, Loftus, and Hammond 2012; L.-A. Leow et al. 2013; Marinelli et al. 2009) and found intact adaptation. Normal adaptation was also found by Isaias et al. (2011) and (Marinelli et al. (2009) [Experiment 2] who tested PDs OFF medication, and by the study of Gutierrez-Garralda et al. (2013) where people with PD were tested before taking their morning medication, therefore suggesting that adaptation itself was not influenced by dopaminergic medication. The VMR study by Marinelli et

al. (2009) found savings to be affected in PDs OFF medication [Experiment 2], which was similarly shown in their first experiment where PDs remained ON medication, as well as by other studies where savings were tested ON meds (Bédard and Sanes 2011; L. A. Leow, Loftus, and Hammond 2012; L.-A. Leow et al. 2013). The only other study that tested for force-field adaptation in PD was done OFF medication and found incomplete error reduction. While this finding is in contrast to the studies above we similarly found incomplete error reduction [Experiment 2] with PDs remaining ON medication, therefore making it unlikely that medication is causing the altered adaptation. Altogether, dopaminergic medication seems not to influence motor adaptation and motor memory.

Our study is the first to test for savings in PD on a force-field adaptation task. Quantification of adaptation using LD showed no group related differences in savings, but we did find some evidence that 1-hour after adaptation FC was more improved in Controls than in the PD group. Apart from this small difference savings were similar between groups, which is surprising since interference was strongly affected in PD. There is a possibility that the overall amount of savings found in our study too low was to observe deficits of savings in people with PD, i.e. there was a floor effect. The group average of LD and FC mainly showed enhanced performance in the beginning of the second adaptation phase when tested for savings, while interference in Controls persisted throughout Adapt 2. The size of interference was therefore substantially larger compared to the measured savings and subsequently could have led more easily to the revelation of deficits in PD. Our statistical design used was sensitive to individual changes and fitted the actual data better than statistical models used by previous studies, though was

therefore also more conservative what could have caused different results from earlier studies looking at savings in PD. Altogether, we do not rule out that deficient consolidation in PD is underlying our results and we believe a different task might be more suitable to clear up our current findings.

In conclusion, opposed to earlier adaptation studies using VMR tasks we did not find an impairment of savings in PD following force-field adaptation. Interestingly, we did find a strong reduction of interference in PD. This discrepancy in results challenges the current idea that motor memory problems in PD are caused by incomplete consolidation of the adapted state due to deficient operant reinforcement mechanisms. In addition, further investigation is required to get a better understanding of the effect of PD pathology on kinematic versus dynamic learning.

Chapter 4

Context-Dependent Force-Field Adaptation in Parkinson's Disease and the Effect of Enhanced Feedback

4.1 Introduction

People with PD show deficits of recall following kinematic motor adaptation as tested with a VMR task (Marinelli et al. 2009; Bédard and Sanes 2011; Leow, Loftus, and Hammond 2012). Although depleted levels of dopamine are known to be the root cause of problems in PD to date it is unclear what faulty mechanism in PD is exactly underlying the deficits in recall. It has been suggested that savings following adaptation (faster relearning on re-exposure to a previously learnt adaptation task) occurs through operant reinforcement mechanisms; a process in which rewarding the correct motor action leads to the strengthening of that response and subsequently the formation of a memory of the adapted state (Huang et al. 2011). The signalling of reward (and punishment) in operant reinforcement is modulated by dopamine in the basal ganglia system (Schultz 2015) and cognitive behaviours driven by these mechanisms have been shown to be affected in PD (Knowlton, Mangels, and Squire 1996; Frank, Seeberger, and O'Reilly 2004; Shohamy et al. 2005). However, behavioural studies linking deficient reinforcement in PD with the known deficits in motor memory are lacking.

The process of adaptation relies heavily on the cerebellum and is normally driven by error (Shadmehr, Smith, and Krakauer 2010), but is also possible using success-based mechanisms (Izawa and Shadmehr 2011). Adaptation using these mechanisms has been shown to lead to more retention of the adapted state (Shmuelof et al. 2012; Galea et al. 2015), proposing a key role of the reward system in reinforcing the adapted state. Gutierrez-Garralda et al. (2013) investigated if people with PD could perform prism adaptation using success-based mechanisms and showed that adaptation was significantly

impaired compared to Controls. Adaptation using error-based learning was unaffected in the PD group, a finding that has been replicated by many others (Marinelli et al. 2009; Bédard and Sanes 2011; Isaias et al. 2011; Leow, Loftus, and Hammond 2012; Leow et al. 2013).

Although it is likely that impaired success-based/reinforcement mechanisms are contributing to the poor recall seen in PD after adaptation, in our previous study using force-field adaptation we showed that, while anterograde interference was strongly reduced, savings were largely intact in PD. Anterograde interference is the phenomenon of impaired adaptation when an opposite adaptation (or other task that interferes) is performed beforehand, i.e. memory of the initial adaptation interferes with learning the second (opposite) adaptation (Shadmehr and Brashers-Krug 1997; Shadmehr and Holcomb 1999; Miall, Jenkinson, and Kulkarni 2004). Operant reinforcement processes are thought to underlie both savings and interference (Huang et al. 2011), but other factors might be contributing to the strength or retrieval of such motor states.

Interference is best known from studies in which two opposite rotations or force-fields are performed in sequence but separated in time and performed in blocks of trials (Brashers-Krug et al., 1996; Miall et al., 2004). Interference has also been shown when the two opposing adaptations are performed in a repeating (Karniel and Mussa-Ivaldi 2002) or random (Osu et al. 2004) alternating interleaved fashion. In these tasks it is impossible to adapt successfully to both perturbations, however, there is a large body of literature showing that if each field is linked to a contextual cue it is possible to learn these fields at the same time (Wada et al., 2003; Osu et al., 2004; Richter et al., 2004;

Hirai et al., 2006; Hwang et al., 2006; Addou et al., 2011; Baldeo and Henriques, 2013; Howard et al., 2013; Wang and Müsseler, 2014; Ayala et al., 2015; Yeo et al., 2015). The observation that contextual information can facilitate the simultaneous learning of two (or more) motor states implies the presence of a neurobiological link between the contextual cue and motor state. Such a link seems closely related to habit formation, which is characterized by the strengthening of the connection between a stimulus or context and an action (Graybiel 2008; Yin and Knowlton 2006), and shown to be impaired in PD (Saint-cyr, Taylor, and Lang 1988; Knowlton, Mangels, and Squire 1996; Ashby et al. 2003). Moreover, results from Nakahara et al. (2004) suggest that the BG incorporate sensorimotor and contextual information when reinforcing motor states.

Although motor adaptation and habits are treated as separate entities, investigating the interface between the two modalities might help us understand what causes disruption of savings and interference in PD. To assess context-dependent motor adaptation in PD we used a task similar to Howard et al. (2013) [experiment 7]. Firstly, we investigated if people with PD showed deficits in context-dependent motor adaptation and whether these deficits carry over into decrements of recall of the adapted state. Context-dependent adaptation was examined by having participants learn to adapt to a randomly alternating force-field while providing direction-specific context. After a 30-minute break participants were tested for recall. If people with PD were less able to link visuo-spatial context to the direction of a force-field our participants with PD would show diminished adaptation compared to Controls. To test sensitivity to reward and punishment we repeated the experiment, but information about success and failure was enhanced by the

addition of auditory feedback. If the enhanced feedback would lead to improved performance in Controls but not people with PD we would expect a larger divide between the groups.

4.2 Materials and Methods

4.2.1 Participants

4.2.1.1 Experiment 1

Ten people with PD (63 ± 3 years, age range 52 – 73, 3 females) and 10 healthy age-matched Controls (69 ± 1 years, age range 64 – 74, 6 females) participated in this experiment. Handedness testing with the Edinburgh Handedness Inventory (Oldfield 1971) confirmed that all twenty participants were right-handed. Cognitive screening was performed with the Oxford Cognitive Screen (OCS) (Demeyere et al. 2015). No cognitive impairments were found as all participants with PD and Controls scored 10 out of 10. Participants were tested on their motor performance using the UPDRS-III (Unified Parkinson's Disease Rating Scale Part III – motor examination). The UPDRS score for the PD group was 26 ± 4, while Controls had a score of 5 ± 1. The PD group had a disease duration of 4 ± 1 years (ranging from 3 months to 10 years).

4.2.1.2 Experiment 2

A total of 20 people took part in experiment 2; 10 people with PD (64 ± 2, age range 51 – 77, 7 females) and 10 Controls (65 ± 1, age range 59 – 71, 6 females). There were 2 left handers in the PD group and 1 left-handed participant in the Control-group. One participant with PD scored 9 out of 10 on the OCS test, the others scored 10 out of 10. The PD group scored 34 ± 3 on the UPDRS and they had a disease duration of 5 ± 2 years (ranging from 10 months – 22 years). UPDRS of Controls was 6 ± 1.

Age ($F(3, 36) = 1.847$, $p = 0.156$), gender ($\chi^2(df = 3, N = 40) = 3.636$, $p = 0.304$), handedness ($\chi^2(df = 3, N = 40) = 3.964$, $p = 0.265$, and OCS ($F(3,36) = 1$, $p = 0.404$) were not different between the 4 groups. As expected, the UPDRS was significantly different; $F(3,36) = 34.374$, $p < 0.001$, which was due to differences between the PD and Control groups. All participants with PD took part while on their normal medication, which included various regimes of PD-related medication; see table 4.1 and 4.2 in Appendix II. All participants gave written informed consent before taking part and the protocols involved were all approved by the appropriate institutional ethics committees.

4.2.2 Experimental Procedure

Participants were seated in front of the vBot (Howard, Ingram, and Wolpert 2009), holding the handle of the robotic manipulandum with which they performed the task (see figure 4.1). The task was displayed on a computer monitor and projected on a semi-silvered mirror that was situated in the horizontal plane immediately above the handle. Movements were performed with the right arm and always took place in front of the body midline, with sight of the arm itself blocked by a blanket. A cursor on the mirror was displayed either 10 cm to the left or right of the midline handle position and using the handle participants were asked to make straight 10 cm movements from the starting point (30 cm distal) to the target (20 cm distal), this was the only movement required of all the participants.

The behavioural protocol contained 4 phases. During the first 200 trials no forces were imposed on the handle, but the cursor display alternated randomly between the left and rightward shift (Baseline; trial 001 – 200), see figure 4.1B. After this baseline phase, the contextual motor adaptation started during which each position of the cursor (left or right) was linked to either the clockwise (CW) or counter clockwise (CCW) force-field for 400 trials (Adapt 1; trial 201 – 600). A 30-minute break followed, before the washout phase began, in which the participants performed 200 trials with the robot motors off (Washout; trial 601 – 800), so that participants returned to baseline levels before being retested and after-effects could be observed. Lastly, another 400 trials of adaptation followed to test if the link between context and force-field was consolidated to memory and had let to improved performance (Adapt 2; trial 801 -1200). Task conditions were identical for both experiment 1 and 2 except the feedback received after each trial completion during baseline and the first adaptation phase.

In experiment 1 whenever the target was reached the target turned yellow, indicating a hit, see figure 4.1D. Movements that terminated outside the target were indicated with a red target instead. In addition, if movements went outside ± 2 cm from the midline the target would turn red, which was to encourage participants to engage with the task and prevent them from reluctantly making movements.

In experiment 2, during baseline and Adapt 1, the yellow target indicating a successful trial was accompanied by a pleasant sound and a visual explosion, mimicking a firework, around the target (see figure 4.1E). The red target, indicating an errorful movement was combined with a buzzer. These enhanced feedback conditions during

Adapt 1 were intended to elicit stronger reinforcement. During washout and Adapt 2 the additional reinforcing feedback was removed and normal feedback conditions applied, so that any carried over improvements in learning could be accounted for entirely by the enhanced feedback during Adapt 1. Movements that took longer than 500 ms to complete were indicated with a "Too slow!" message at the top of the screen, both during Experiment 1 and 2.

To test for contextual motor learning the alternating CW and CCW force-fields were always associated with a consistent visuospatial shift of the task; to the left or right. The relationship between the visuospatial context and force direction were counterbalanced between participants so that half of the participant experienced a left shift with a CCW force and a right shift with the CW force, the other half experienced the opposite relationship. The strength of both force-fields was 12 N/m/s. By learning the link between the visuospatial context and direction of force participants could learn to compensate for both force-fields simultaneously and reduce their overall error. The same direction of force was never repeated more than four times.

No explicit information or instruction was given about the link between the direction of force and the context. Afterwards, each participant was asked whether they had noticed the relationship between the context and direction of force, which provided an indication about their explicit knowledge at the end of the experiment.

To capture the compensatory force applied by the participants to counter the force-field error-clamp trials were inserted among all phases. In error-clamp trials movement was constrained to a virtual channel between the start position and the target, the lateral

forces that the participant produced during these trials can be measured as the force applied against the walls of the channel. Every 20 trials 2 error-clamp trials took place, of which one captured adaptation to the CW field and the other adaptation to the CCW field. The position and order of these error-clamp trials were pseudo-randomly alternated. Importantly, an error-clamp trial always took place after a change in context had occurred, never after a repetition. This arrangement allowed measurement of the force compensation elicited by appearance of the context without the influence of improvements due to the previous trial.

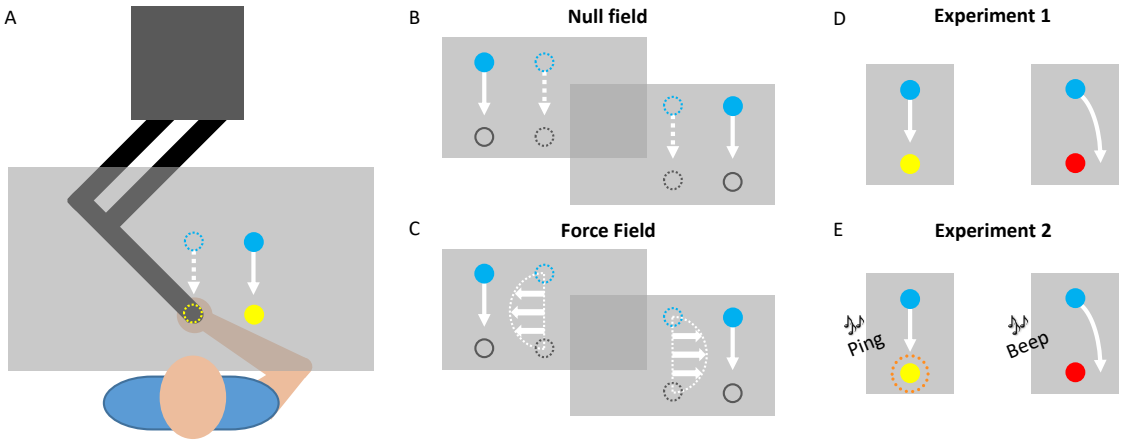


Figure 4.1 Experimental set-up and task specifics. A) Participants held the handle of the vBot and made reaching movements from the starting point (blue) to the target (yellow). Movements were made in the body midline (indicated with dotted circles and arrow), but the starting point, cursor and target were shifted 10 cm leftwards and rightwards of the midline as can be seen in A), B) and C) (solid circles and arrows). B) During baseline and washout no forces were imposed on the handle. Participants still experienced left and rightwards shifts. C) Participants experienced CW and CCW force-fields during adaptation (and re-adaptation), which were accompanied with direction specific shifts. The combination of shift and direction of force-field was counterbalanced between subjects. D) In experiment 1 a HIT was indicated by a yellow target and a MISS by a red target. E) In experiment 2 an explosion and pleasant sound also appeared during a HIT, while an unpleasant sound was heard for a MISS.

4.2.3 Data Analysis

The main measures of performance were; lateral deviation (LD) and force compensation (FC) ratio. Using MATLAB (The MathWorks, Version R2016b) LD at peak velocity was calculated and sign adjusted, so that errors for CW and CCW forces had the same sign. Within each group outliers (values outside mean ± 2*standard deviations) were removed for each trial, which led to the removal of ~3% of LD trials (Exp 1- Controls: 2.6% (1.7% miss trials, 0.9% hit trials); PD: 3.4% (2.5% miss, 0.9% hit); Exp 2 – Controls: 3.0% (1.3% miss, 1.7% hit); PD: 3.1% (2.0% miss, 1.1% hit)). After outlier removal LD was averaged in blocks of 10 trials. FC ratio, was calculated from the error-clamp trials. During an error-clamp trial with lateral error clamped at zero the lateral forces produced by the participant were recorded (i.e. the actual force). To obtain the FC-ratio of each error-clamp trial the actual force was compared to the ideal force (equation 4.1). The ideal force was calculated by multiplying the velocity during an error-clamp trial with the field constant; 12 N/m/s. The ideal force is the force that the participant should produce in order to completely compensate for the force exerted on their hand.

$$FC = \frac{\int_{t_0}^{t_{end}} actual\ Force}{\int_{t_0}^{t_{end}} ideal\ Force} \times 100\% \qquad \text{[eq. 4.1]}$$

Integration for both for the actual and ideal force was carried out from the start till the end of the trial, i.e. from t_0 till t_{end},. The start and end of the trial were defined as the time point that the velocity during the error-clamp trial went above and below 4 cm/s, respectively. Outliers of FC were removed (values outside mean ± 2*SD), which led to

the removal of 3-4% of FC trials (Exp 1 – Controls: 3.1% (all hit trials); PD: 3.5% (0.5% miss trials, 3.0% hit trials); Exp 2 – Controls: 3.2% (all hit trials); PD: 4% (0.1% miss, 3.9% hit)). Hereafter FC was averaged in blocks of 2 trials.

Due to the known issues with perseveration in PD (Stoffers et al. 2001) we wanted to assess differences between performance following different repeat-switch patterns of the two contexts at the group level in Adapt 1. Eight repeat-switch sequences were identified and isolated from the first adaptation phase (R = rightward shift, L = leftward shift): RRLL, RRRL, RLLL, RLRL, and their counterparts LLRR, LLLR, LRRR, and LRLR. The latter four sequences were collapsed with their counterpart (e.g. RRLL + LLRR) and the LD reported using the former notation. For the RRLL-sequence a total of 40 repeats was found, for which the LD was averaged for each group separately. The averaging was similarly done for the other sequences, but there were 36 (RRRL and RLLL) and 37 (RLRL) repeats.

4.2.4 Statistical Analysis

Group differences in LD and FC during initial adaptation (Adapt 1) and re-adaptation (Adapt 2) were tested with a LME model for experiment 1 and 2 separately. The LD (Adapt 1: blocks 21 – 60, Adapt 2: blocks 81- 120) and FC data (Adapt 1: blocks 11 – 30, Adapt 2: blocks 41 - 60) were fitted with a LME model in RStudio (R Core Team 2016) using the lme4 package (Bates et al. 2015). The models included fixed effects *group*, *phase*, and a 2nd degree polynomial function using the continuous variable *block*, i.e. *polynomial(block)* containing *block* and *block*^{2}. *Subject* was added as a random effect in

a way that allowed intercept, gradient and curvature to change per subject within phase 1 and 2. Using the Maximum Likelihood method, the model was fitted to the data. Equation 4.2 shows the LME model, DV (dependent variable) representing either the LD or FC data.

$$DV \sim group \times phase \times polynomial(block, 2) + (phase \times polynomial(block, 2) \mid subject) \quad \text{[eq. 4.2]}$$

For experiment 1 and 2 the LD-model and FC-model had an R^2 of 0.781 and 0.699 and 0.743 and 0.577, respectively, suggesting that between ~60 - 80% of the variance was explained by these models. To assess main and interaction effects of the fixed factors F-tests were performed using the Satterthwaite approximation of degrees of freedom. Significant interaction effects were followed by Bonferroni adjusted post-hoc analysis on the estimated marginal means.

Prior to testing differences in adaptation, the end of baseline and end of washout (average last two blocks of LD [blocks 19-20 and 79-80], and FC [blocks 9-10 and 39-40]) were tested for group differences using a validation model that included the fixed factors *group* and *phase* (baseline vs. washout) and the random factor *subject*.

To assess retention of the context-dependent adaptation an LME model was fitted to the LD data (block 61 - 80) and the FC data (block 31 – 40) of de-adaptation. The model was similar to equation 4.2, but phase was excluded from the fixed and random effects. F-tests were performed to reveal main and interaction effects.

Repeat-switch patterns, percentage of MISS trials, peak velocity (PV), and PV position (y-pos) were also tested for group differences using a mixed model including fixed effects *group* and *sequence*/*phase,* and *subject* as random effect.

4.3 Results

4.3.1 Experiment 1

We found that people with PD were less able to reduce their LD during the adaptation phases of the context-dependent adaptation task compared to Controls, but both groups showed improved LD reduction during re-adaptation. FC was initially similar between the groups, but was reduced in the PD group later into adaptation. In addition, Controls showed an increase in FC during re-test, while such improvement was less present in people with PD.

4.3.1.1 Performance during baseline and washout was similar between groups

Participants performed 200 trials of baseline movements with the robot motors off, before exposure to the force-fields. During baseline, participants experienced the randomly alternating left and right visual contexts and were required to make straight lines from start to target always in the midline. Switching between the two contexts had no effect on the PD group as their LD and FC were around zero and similar to Controls (Figure 4.2 and 4.3). The end of baseline was compared to the end of washout to make sure that both the adaptation and re-adaptation phase started from a similar level. Statistical tests confirmed that the LD (R^2 = 0.723) and FC (R^2 = 0.641) at the end of baseline and washout similar was between groups. No main effect of *group* (LD: F(1, 20.0) = 0.141, p = 0.711; FC: F(1, 20.0) = 0.404, p = 0.532) or *phase* (*baseline vs. washout;* LD: F(1, 20.0) = 4.310, p = 0.051; FC: F(1, 20.0) = 2.474, p = 0.131), nor an interaction effect of *group*

× *phase* (LD: F(1, 20.0) = 1.370, p = 0.256; FC: F(1, 20.0) = 1.369, p = 0.256) was observed. As such, both groups started both adaptation phases with the same levels of error.

4.3.1.2 Reduction of LD was larger in Controls vs. PD

At the start of the adaptation phase both groups showed similar deviation to the force-field. LD (block 21) was 1.4 ± 0.1 cm for the PD group and 1.3 ± 0.2 cm for Controls. Hereafter, LD declined more rapidly in Controls. Mid-adaptation (average block 40– 41) the PD group displayed an error of 1.1 ± 0.1 cm, while Controls had reduced their error to 0.8 ± 0.1 cm. The divide between the groups continued. At the end of adaptation (block 60), the LD of the PD and Control group was 1.0 ± 0.1 cm and 0.7 ± 0.2 cm, respectively. During re-adaptation the PD group showed similar behavior to the initial adaptation; their LD (block 81) was 1.4 ± 0.1 cm which then slowly declined to 0.9 ± 0.2 cm (block 120). In contrast, the Controls started off with an error of 1.2 ± 0.1 cm, which was slightly lower than the initial adaptation. They then rapidly reduced their error to levels comparable to the end of Adapt 1 and ended with an LD of 0.7 ± 0.2 cm. Individual trajectories are shown in figure S3 (Appendix I).

Statistical tests on the LD data (LME fit R^2 = 0.781) did not show significant group differences, but it did reveal a trend for *group*: F(1, 20.1) = 3.915, p = 0.062. The trend indicates an overall difference between the PD and Control group both during Adapt 1 and 2, which is also seen in Figure 4.2. A main effect for *phase*; F(1, 20.1) = 10.300, p = 0.004, but no *group* × *phase* interaction effect; F(1, 20.1) = 0.537, p = 0.472, was found,

suggesting that the intercept of LD changed from Adapt 1 to Adapt 2, but this change was similar between the groups. A *phase* × *block* interaction effect was also found; F(2, 27.7) = 7.656, p = 0.002, which seemed due to the curvature; t(19.7) = -2.975, p = 0.015, and not the slope; t(21.9) = -1.633, p = 0.234, of adaptation. The absence of a *group* × *phase* × *block* effect (F(2, 27.7) = 1.572, p = 0.226) implies that this change in curvature from Adapt 1 to Adapt 2 similar was between the groups. Altogether, it seems that people with PD are less able to reduce their LD during the context-dependent task in comparison to Controls, both during initial and secondary adaptation. In addition, adaptation was improved in both groups during Adapt 2.

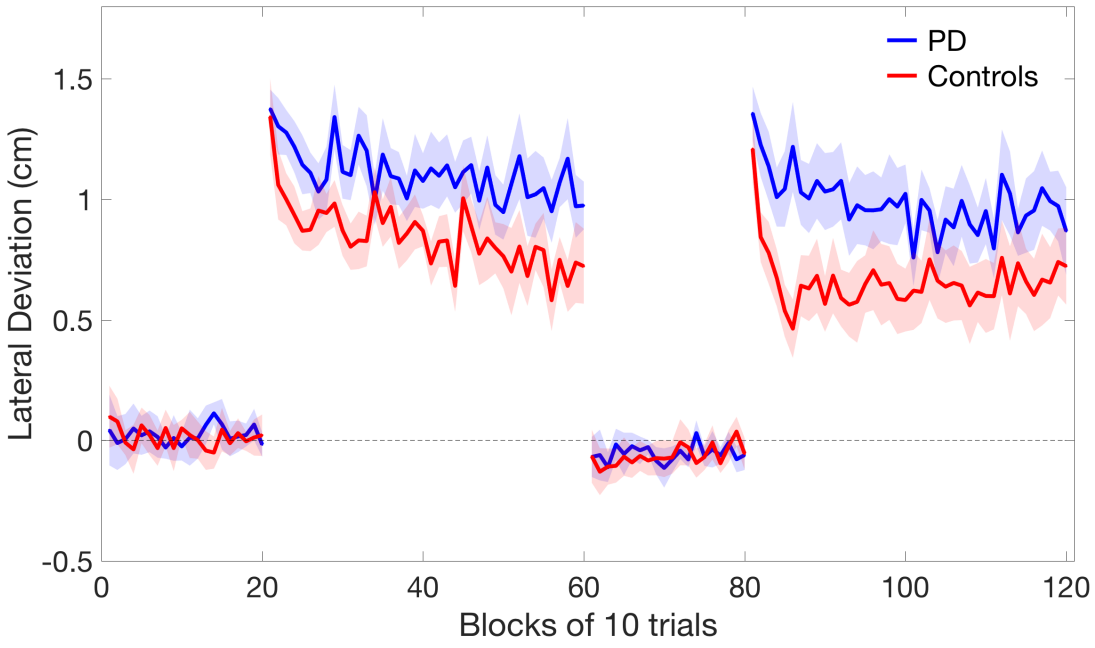


Figure 4.2 Experiment 1 - Lateral Deviation (LD) of the PD (blue) and Control group (red) for Baseline (block 1 – 20), Adapt 1 (block 21 – 60), Washout (block 61 – 80), and Adapt 2 (block 81 – 120). A 30-minute break took place between Adapt 1 and the Washout phase.

4.3.1.3 Controls showed improved FC during secondary exposure

Error-clamp trials were interspersed among the normal trials and always took place after a change of context had occurred. As expected, at the start of Adapt 1 this resulted in a negative FC for both groups. Despite the change in context, participants were counteracting the force-field they just had experienced instead of the force-field associated with the context. However, as the adaptation phase continued the FC turned positive, indicating that participants learned to anticipate each force-field using the visuospatial context.

At the start of Adapt 1, both groups showed similar behaviour during the error-clamp trials. Force compensation for the PD and Control group started off (block 11) with negative values of -28.0 ± 7.2 % and -27.5 ± 5.8 %, respectively. Mid-adaptation (average block 20 – 21) FC was increased to 25.1 ± 10.0 % in the PD group and 34.6 ± 10.2 % in the Control group. The FC fluctuated in both groups, but while Controls managed to end the adaptation (block 30) with an FC of 39.1 ± 11.5 %, the PD-group only learned to compensate for 17.1 ± 20.0 % of the force-field, although the standard error revealed that the FC differed substantially among PD participants. The difference between PDs and Controls became more apparent during the second adaptation (see Figure 4.3).

Controls started the re-adaptation with an FC of -1.0 ± 5.5 % after which compensation quickly increased to values above those reached during the initial adaptation. After some variation in FC Controls ended re-adaptation with 34.8 ± 12.0 % compensation. In contrast, performance of the PD group was more impaired. They started

the second adaptation with 5.2 ± 8.6 % force compensation, which then reached over 20% several times before ending with an FC of 14.4 ± 13.8 %.

F-tests on the LME model of the FC data ($R^2 = 0.699$) showed no main effect of *group*; $F(1, 20.0) = 1.270$, $p = 0.273$, revealing no overall difference of FC between the PD and Control group during Adapt 1 and 2. However, a main effect of *phase* ($F(1, 21.1) = 19.036$, $p < 0.001$) and an interaction effect of *group* × *phase* ($F(1, 21.1) = 5.230$, $p = 0.033$) was found. Bonferroni adjusted post-hoc analysis revealed that these effects were due to a significant difference between Adapt 1 and 2 in the Control group; $t(20.62) = -3.473$, $p = 0.009$, but not the PD group; $t(20.62) = -0.060$, $p = 1.000$. No direct group differences were found between the PD and Control group for Adapt 1; $t(22.1) = -0.673$, $p = 1.000$, or Adapt 2 ;$t(22.1) = -1.481$, $p = 0.611$. In addition, a *phase* × *block* effect ($F(2, 33.3) = 23.468$, $p < 0.001$), but no *group* × *phase* × *block* interaction ($F(2, 33.3) = 0.235$, $p = 0.792$ was found, with post-hoc tests showing; slope: $t(20.6) = 6.237$, $p < 0.001$; and curvature: $t(21.0) = -1.381$, $p = 0.364$, indicating that the slope of adaptation was changed in both groups. Overall, these results show relatively preserved force compensation in PD, but Controls showed more improvement of FC during re-adaptation.

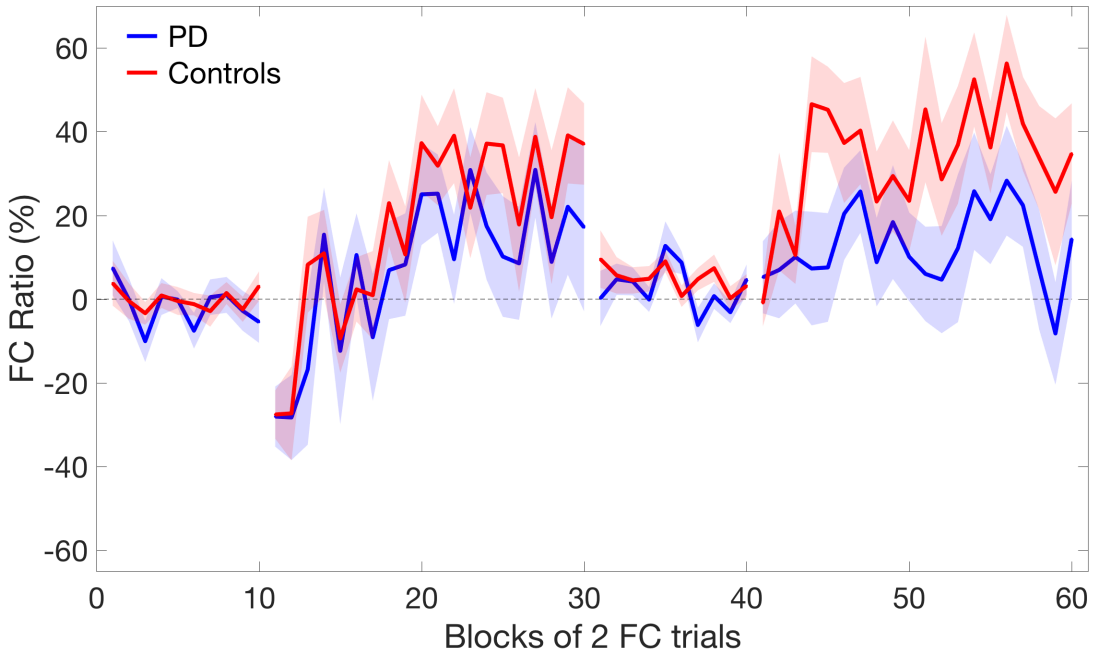


Figure 4.3 Experiment 1 - Force Compensation during Baseline (block 1 – 10), Adapt 1 (block 11 – 30), Washout (block 31 – 40), and Adapt 2 (block 41 – 60) for the PD (blue) and Control (red) group. A 30-minute break took place between Adapt 1 and the Washout phase.

4.3.2 Experiment 2

When reinforcement during the context-dependent adaptation task was strengthened using enhanced feedback a large divide between the groups was revealed. The PD group was worse at reducing their deviation compared to Controls and showed no improvement during re-adaptation. People with PD were also less able to learn to compensate for the force, although both groups showed some improvements of FC during Adapt 2.

4.3.2.1 Both groups showed similar behaviour in baseline and washout

At the end of baseline both groups showed an LD and FC around zero, which indicated that people with PD, as well as Controls, did not have any problems with switching between the two contexts in absence of the force-field. Statistical tests (LD: $R^2 = 0.788$; FC: $R^2 = 0.459$) showed no significant differences for *group*; LD: $F(1, 20.0) = 0.395$, $p = 0.537$; FC: $F(1, 20) = 0.750$, $p = 0.397$, *phase*; LD: $F(1, 20.0) = 2.932$, $p = 0.102$; FC: $F(1,2\ 20) = 0.755$, $p = 0.395$, and *group* × *phase*; LD: $F(1, 20.0) = 0.393$, $p = 0.538$; FC: $F(1, 20) = 1.588$, $p = 0.222$. The latter two tests confirm that both groups returned to baseline levels at the end of de-adaptation.

4.3.2.2 The PD group showed impaired reduction of LD

At the start of the first adaptation phase the PD and Control group showed an LD (block 21) of 1.6 ± 0.1 cm and 1.3 ± 0.1 cm, respectively. A quick drop in LD followed in both groups, after which error consistently declined to 0.9 ± 0.1 cm in the PD group and 0.4 ± 0.1 cm in Controls (block 60), see figure 4.4. Re-exposure of the force-field to Controls resulted in an LD of 0.9 ± 0.1 cm (block 81), which was then rapidly reduced to levels with which Controls ended the initial adaptation. They ended re-adaptation with an error of 0.3 ± 0.1 cm (block 120). The PD group performed worse during re-adaptation. Although their LD was initially improved compared to the first adaptation; 1.3 ± 0.1 cm, not much further improvement took place; LD measured during block 120: 1.1 ± 0.2 cm. Individual trajectories are shown in figure S4.

F-tests on the LME model ($R^2 = 0.743$) confirmed the difference in LD between the PD and Control group as a main effect of *group* was found; $F(1, 20.0) = 28.398$, $p < 0.001$. A main effect of *phase*; $F(1, 20.1) = 35.183$, $p < 0.001$, and *group* × *phase* interaction; $F(1, 20.1) = 21.578$, $p < 0.001$, were also found. Bonferroni adjusted post-hoc analysis revealed a significant difference between the PD and Control group both for Adapt 1; $t(22.2) = 3.804$, $p = 0.004$, and Adapt 2; $t(21.9) = 5.130$, $p < 0.001$. Post-hoc analysis also showed a strong significant difference between Adapt 1 and 2 in Controls; $t(21.0) = 6.310$, $p < 0.001$, but not in the PD group; $t(21.0) = 1.473$, $p = 0.625$. These results indicate a strong impairment of LD reduction in PD compared to Controls during the initial and secondary adaptation phase. Furthermore, Controls showed improved LD reduction during re-exposure, which was not found for the PD group. In addition, statistical tests showed that the curvature of adaptation changed from Adapt 1 to Adapt 2 in both groups as a *phase* × *block* interaction; $F(2, 22.1) = 27.399$, $p < 0.001$, but no *group* × *phase* × *block* effect was found; $F(2, 22.1) = 0.681$, $p = 0.516$, with curvature; $t(19.7) = -2.975$, $p = 0.015$, and slope; $t(21.9) = -1.633$, $p = 0.234$.

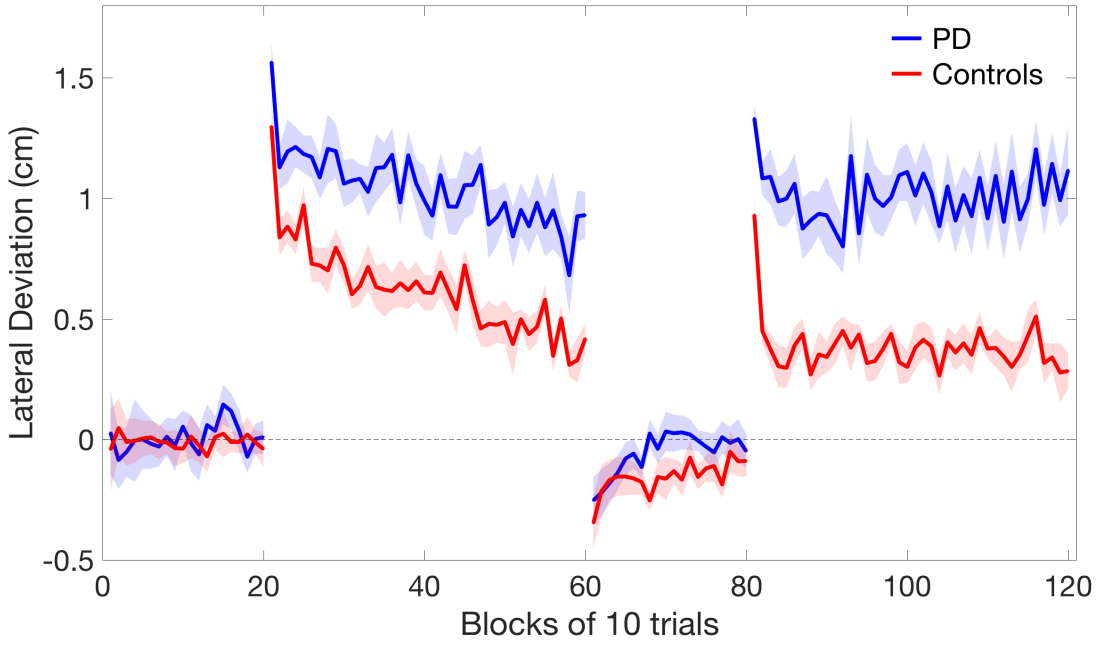


Figure 4.4 Experiment 2 - Lateral Deviation (LD) of the PD (blue) and Control group (red) for Baseline (block 1 – 20), Adapt 1 (block 21 – 60), Washout (block 61 – 80), and Adapt 2 (block 81 – 120). A 30-minute break took place between Adapt 1 and the Washout phase.

4.3.2.3 Force Compensation was worse in the PD group

When the force-field was introduced both the PD and Control group started with a comparable negative FC (block 11); -20.4 ± 12.9 % vs. -21.7 ± 8.5 %, respectively (see figure 4.5). Hereafter, the PD group reached an FC (average block 20 – 21) of 25.9 ± 9.0 % halfway through adaptation, and an FC of 19.8 ± 11.1 % (block 30) at the end of adaptation. In contrast, the Control group reached 40.9 ± 10.0 % FC mid-adaptation and 38.5 ± 10.7 % at the end of adaptation, showing improved performance compared to the PD group. During re-adaptation Controls started with an FC of 5.0 ± 4.8 % (block 41), after which FC increased to levels with which the first adaptation was ended. The level

of FC was maintained and they ended the second adaptation with an FC of 51.3 ± 10.7 % (block 60). FC at the start of re-adaptation was -4.7 ± 3.1 % in the PD group. Although it initially increased, the PD group ended the re-adaptation with only 7.2 ± 13.0 % force compensation.

Statistical tests on the FC data (LME fit $R^2 = 0.577$) confirmed that there was an overall difference between the PD and Control group, both during Adapt 1 and 2, as a main effect of *group* was found; $F(1, 20.0) = 6.341$, $p = 0.020$. *Phase* was not significant; $F(1, 20.0) = 3.454$, $p = 0.078$, but did reveal a trend, and no *group* × *phase* interaction was found; $F(1, 20.0) = 1.485$, $p = 0.237$, suggesting that there might be some improvements of the intercept of FC in both groups during re-exposure. However, a *phase* × *block* effect was also found; $F(2, 30.4) = 12.890$, $p < 0.001$, with post-hoc tests revealing mainly a difference in the slope; $t(21.7) = 4.733$, $p < 0.001$; rather than the curvature; $t(19.9) = -2.159$, $p = 0.087$, in both groups. The difference in slope was due to a decline as the increase in FC was less steep as during the first adaptation phase. In summary, overall force compensation was reduced in people with PD compared to Controls, but both groups seemed to show some improvements of FC during Adapt 2.

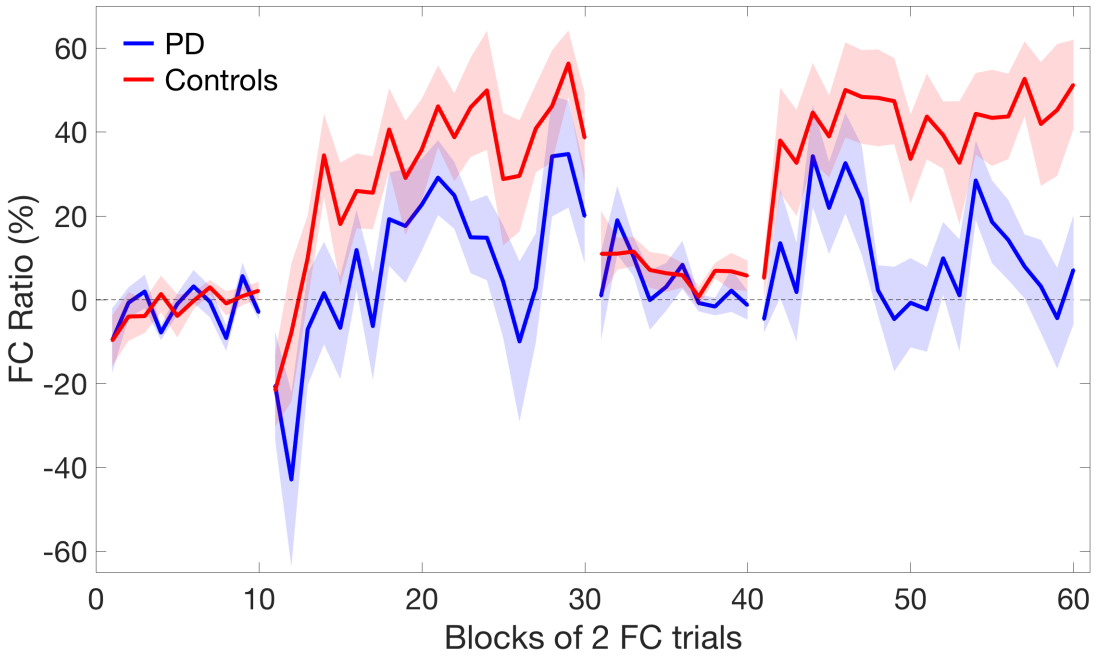


Figure 4.5 Experiment 2 - Force Compensation during Baseline (block 1 – 10), Adapt 1 (block 11 – 30), Washout (block 31 – 40), and Adapt 2 (block 41 – 60) for the PD (blue) and Control (red) group. A 30-minute break took place between Adapt 1 and the Washout phase.

4.3.3 Observed power

Despite substantial group differences in LD for experiment 1 as shown in figure 4.2 no significant group differences were found, which might be due to low power. In R using the powerSim-function from the simr-package the observed power for the fixed effect *group* was calculated for the LD and FC data of experiment 1 and 2 at $\alpha = 0.05$. Observed power is the estimate of the power based on the observed effect size.

For experiment 1 the fixed effect *group* showed an observed power of 56.00% (45.72 - 65.92 [95% confidence interval]) for LD based on the observed effect size of 0.15. FC had an effect size of -7.6 for *group*, which led to an observed power of 23.00% (15.17 - 32.49 [95% CI]). For experiment 2, an observed power of 100.0% (96.38 - 100.00

[95% CI]) was found for LD for an observed effect size of 0.26 for *group*. The fixed effect *group* showed an effect size of -13 for FC with an observed power of 83.00% (74.18 - 89.77 [95% CI]).

4.3.4 Both groups of experiment 2 showed retention of LD

Adaptation to the context-dependent force-field using normal feedback (Experiment 1) did not lead to any significant retention after 30-minutes. Adaptation using enhanced feedback (Experiment 2) resulted in retention of LD, but not FC, in both groups.

After the initial adaptation phase a 30-minute break followed after which participants performed 200 trials of de-adaptation followed by 400 trials of re-adaptation. The de-adaptation phase drove participants to close-to-zero baseline levels before re-adapting to the context-dependent force-field. It also allowed to measure retention of the adaptation. Both the LD and FC revealed very little retention for experiment 1. The deviation in the PD and Control group was negative, but very close to zero; PD: -0.1 ± 0.1 cm; Controls: -0.1 ± 0.1 cm (block 61). Statistical tests (R^2 = 0.624) showed that there was no main effect of *group*; F(1, 20.0) = 0.0192, p = 0.891, or *block*; F(2, 27.3) = 1.063, p = 0.359, nor an interaction effect of *group* × *block*; F(2, 27.3) = 0.674, p = 0.518. Initial retention of FC as measured during block 31 was higher in the Control group than the PD group; 9.6 ± 6.9 % vs. 0.2 ± 6.6 %, but overall de-adaptation did not reveal any main effects (LME fit R^2 = 0.378); *group*: F(1, 19.7) = 0.560, p = 0.463; *block*: F(2, 33.5) = 1.630, p = 0.211, or interaction effect; *group* × *block*: F(2, 33.5) = 0.223, p = 0.801.

Experiment 2 yielded more retention in both groups, for LD, see washout phase figure 4.4 and 4.5. The PD and Control group showed both an LD (block 61) of -0.3 ± 0.1 cm, which was more than for experiment 1. Statistics confirmed the presence of significant retention for LD (R^2 = 0.702), as a main effect of *block* was found; F(2, 30.276) = 20.082, p < 0.001. No main effect of *group* was revealed; F(1, 20.0) = 1.661, p = 0.212, nor a *group* × *block* interaction was shown; F(2, 30.3) = 2.502, p = 0.099. FC at the start of de-adaptation was again higher in Controls; 10.9 ± 10.2 %, than in the PD group; 0.8 ± 10.5 %. However, no significant retention or group differences were shown for FC (R^2 = 0.512); *group*: F(1, 20.0) = 0.455, p = 0.508; *block*: F(2, 37.0) = 2.345, p = 0.110; *group* × *block*: F(2, 37.0) = 0.735, p = 0.486.

4.3.5 The direct effect of enhanced feedback on performance

The results presented above show that context-dependent motor adaptation using enhanced feedback led to better performance in Controls compared to the PD group. Experiment 1 also shows a divide, but this divide between the groups is not as strong as during experiment 2. The results therefore imply that providing enhanced feedback has a beneficial effect over the 'normal' feedback on performance in Controls, while in the PD group no such benefit seems to exist. To investigate the direct effect of feedback on performance in the Control and PD group we decided to do a comparison between experiment 1 and experiment 2. Data from both experiments was collapsed and distinguished in the LME model using an additional fixed effect 'experiment'.

Results on the LD ($R^2 = 0.767$) and FC data ($R^2 = 0.636$) showed no main effect of *experiment* (LD: F(1, 40.0) = 2.351, p = 0.133; FC: F(1, 40.0) = 0.304, p = 0.584), nor an interaction of *experiment* × *group* (LD: F(1, 40.0) = 1.715, p = 0.198; FC: F(1, 40.0) = 0.455, p 0.504), *experiment* × *phase* (LD: F(1, 40.0) = 0.145, p = 0.705; FC: F(1, 40.0) = 0.908, p = 0.346), or *experiment* × *group* × *phase* (LD: F(1, 40.0) = 1.725, p = 0.197; FC: F(1, 40.0) = 0.088, p = 0.767). An overall main effect of *group* (LD: F(1, 40.0) = 21.162, p < 0.001; FC: F(1, 40.0) = 5.975, p = 0.019), and *phase* (LD: F(1, 40.0) = 29.480, p < 0.001; FC: F(1, 40.0) = 16.329, p < 0.001), as well as a *group* × *phase* interaction (LD: F(1, 40.0) = 6.971, p = 0.012; FC: F(1, 40.0) = 5.391, p = 0.025), was found. For LD post-hoc tests showed a significant difference between the PD and Control group both for Adapt 1 (t(44.5) = 3.669, p = 0.002) and Adapt 2 (t(44.4) = 4.164, p < 0.001). In addition, both groups showed improved LD reduction from Adapt 1 to Adapt 2 (PD: t(43.9) = 2.670, p = 0.042; Controls: t(43.9) = 5.811, p < 0.0001), but interaction plots showed a larger reduction of LD during Adapt 2 in Controls leading to the interaction effect. Post-hoc analysis on the *group* × *phase* interaction of the FC data revealed a group difference for Adapt 2; t(44.1) = -2.844, p = 0.027, but not Adapt 1; t(44.4) = -1.768, p = 0.336. In addition, the Control group showed significant improvement in FC from Adapt 1 to Adapt 2; t(43.6) = -2.822, p = 0.029, while the PD group failed to show such improvement; t(43.4) = 0.450, p = 1.000.

Due to a priori assumptions regarding the effect of feedback on each group based on our initial results we performed post-hoc analysis on the *experiment* × *group* interaction. For Controls LD was not significant, but did show a trend; t(44.5) = 1.717, p

= 0.093, while for PDs LD was t(44.5) = 0.030, p = 0.976. FC showed t(44.3) = - 0.721, p = 0.475 for Controls and t(44.3) = 0.156, p = 0.887 for the PD group. A significant effect of enhanced success-based feedback on performance in Controls was not confirmed, but the results of LD suggest there might be an effect, although only weakly indicated.

4.3.6 Response to repeat-switch patterns of context

Due to the known issue with perseveration in PD we assessed the LD of different repeat-switch sequences to make sure that impaired response patterns in PD were not underlying the differences in LD found between the groups, see figure 4.6. The PD and Control group from experiment 1 displayed a similar pattern of responses to the different repeat-switch sequences, but the overall LD was larger in the PD group. However, the analysis of the repeat-switch patterns (i: $R^2 = 0.844$; ii: $R^2 = 0.771$; iii: $R^2 = 0.811$; iv: $R^2 = 0.927$) did not reveal any main effects of *group* for sequence i ($F(1, 20.0) = 2.518$, $p = 0.128$), ii ($F(1, 20.0) = 3.501$, $p = 0.076$), iii ($F(1, 20) = 3.013$, $p = 0.098$), and iv ($F(1, 20) = 2.917$, $p = 0.103$). Also, no group × sequence differences were found for all sequences; i: $F(3, 60.0) = 0.284$, $p = 0.837$; ii: $F(2, 60.0) = 0.600$, $p = 0.618$; iii: $F(3, 60) = 0.053$, $p = 0.984$; and iv: $F(3, 60) = 0.431$, $p = 0.732$.

The PD group from experiment 2 showed patterns, which were comparable to those from experiment 1. Controls from experiment 2 also displayed logical increases and decreases in LD following the repeat-switch sequences, but due to their improved performance the response patterns were flatter compared to the PD group. All sequences

(i: $R^2 = 0.812$; ii: $R^2 = 0.778$; iii: $R^2 = 0.788$; iv: $R^2 = 0.946$) showed a main effect of *group* (i: $F(1, 20.0) = 13.658$, $p = 0.001$; ii: $F(1, 20.0) = 14.206$, $p = 0.001$; iii: $F(1, 20.0) = 15.097$, $p < 0.001$; iv: $F(1, 20.0) = 14.998$, $p < 0.001$). A *group* × *sequence* effect was only shown for sequence iv; $F(3, 60.0) = 2.797$, $p = 0.048$, but not for the other sequences; i: $F(3, 60.0) = 2.114$, $p = 0.108$; ii: $F(3, 60.0) = 1.700$, $p = 0.177$; iii: $F(3, 60.0) = 2.006$, $p = 0.123$.

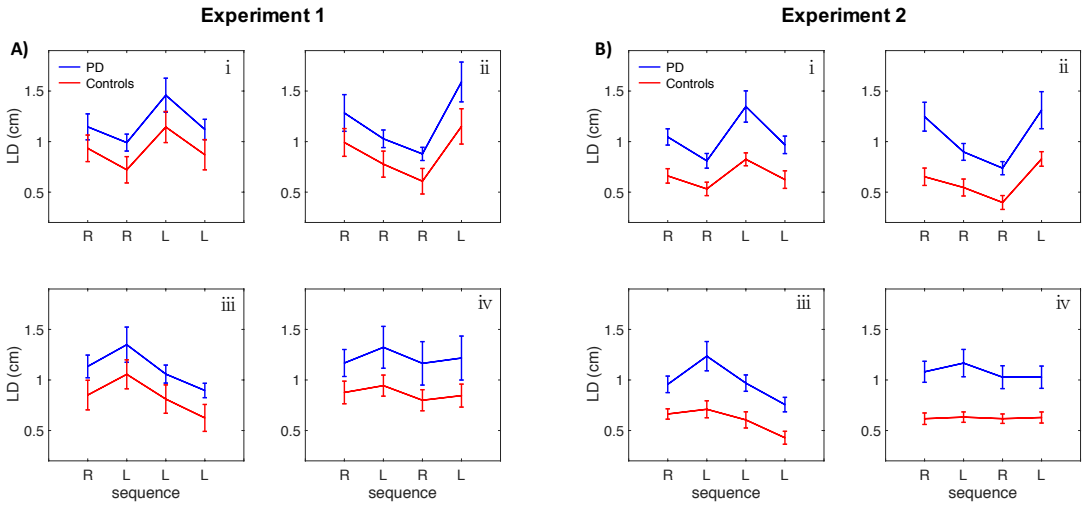


Figure 4.6 Repeat-switch response patterns of the PD group (blue) and Controls (red) shown for experiment 1 (A) and experiment 2 (B). LD was averaged over 4 different sequences (i – iv) and displayed as the mean + SEM.

4.3.7 Percentage of MISS trials was different between the PD and Control group of Experiment 2

As expected, both groups showed an increase in MISS trials during Adapt 1 and 2, see figure 4.7. During baseline and washout the percentage of MISS trials was close to zero.

The PD group of both experiment 1 and 2 showed a higher percentage of MISS trials compared to Controls, but for experiment 1 ($R^2 = 0.637$) no main effect of *group*; $F(1, 20) = 1.727$, $p = 0.204$, nor a *group* × *phase* interaction effect; $F(3, 60) = 1.418$, $p = 0.246$, was found, but a main effect of *phase* was present; $F(3, 60) = 26.940$, $p < 0.001$.

For experiment 2 ($R^2 = 0.687$) a significant effect of *group* was revealed; $F(1, 20.0) = 12.024$, $p = 0.002$, a main effect of *phase*; $F(3, 60.0) = 29.495$, $p < 0.001$, and a *group* × *phase* interaction effect; $F(3, 60.0) = 6.945$, $p < 0.001$. Post-hoc tests showed the interaction was due to a difference between the PD and Control group during Adapt 1; $t(71.0) = 3.199$, $p = 0.033$, and Adapt 2; $t(71.0) = 4.774$, $p < 0.001$, but not baseline; $t(71.0) = 0.556$, $p = 1.000$, or washout; $t(71.0) = 0.469$, $p = 1.000$.

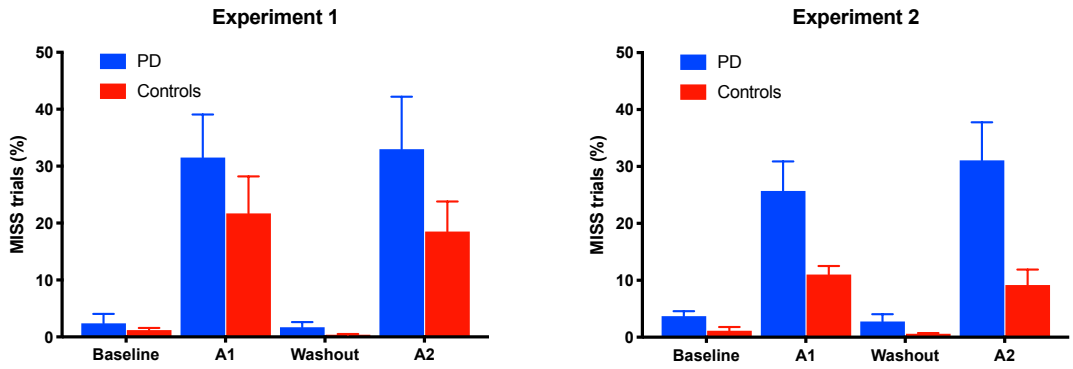


Figure 4.7 Overall percentage of MISS trials for baseline, Adapt 1 (A1), washout, and Adapt 2 (A2) for the PD (blue) and Control (red) group during experiment 1 (left plot) and experiment 2 (right plot).

Further analysis showed that the MISS trials were mostly due to participants exceeding the ±2 cm boundary from the midline, rather than failing to land in the target, see figure 4.8. Exceeding the 2cm-boundary was dependent on the maximum LD (Max LD) for

every trial. Figure 4.9 shows that Max LD was significantly correlated with the LD at PV; $r = 0.92$, $p < 0.001$. Only a small part of MISS trials were due to missing the target. End accuracy as measured with end LD (LD at the level of the target) was also correlated with LD at PV; $r = 0.55$, $p < 0.001$. Altogether, these results show that both Max LD and End LD, of which mainly the former forms a fundamental aspect of whether you were rewarded or punished, highly link to LD at PV (displayed in figure 4.2 and 4.4).

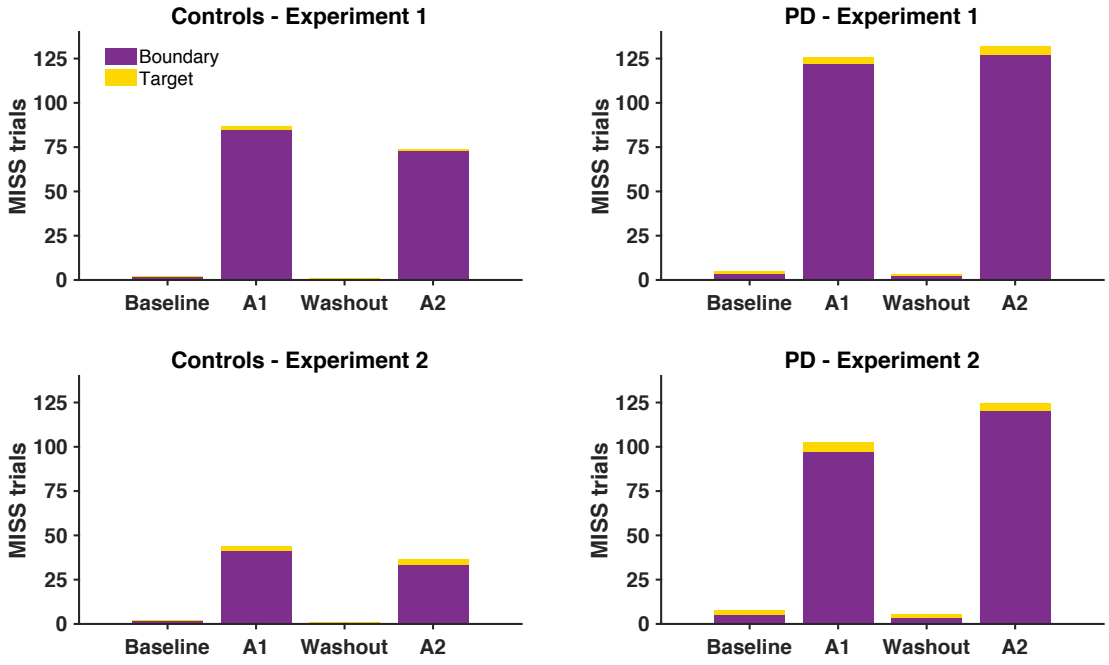


Figure 4.8 Number of MISS trials due to exceeding the ±2cm boundary (purple) or missing the target (yellow) for Controls (left plots) and the PD groups (right plots) for Experiment 1 (top row) and Experiment 2 (bottom row), separately shown for Baseline, Adapt 1 (A1), Washout phase, and Adapt 2 (A2).

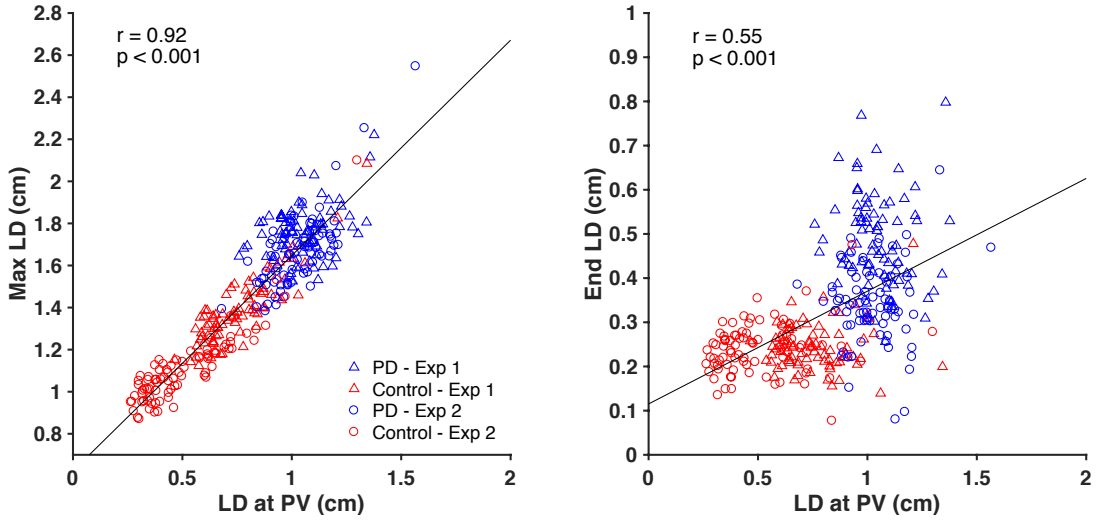


Figure 4.9 Correlation plots of the LD at peak velocity (LD at PV) and the maximum LD (max LD) [left plot] and the LD at PV and the end accuracy (end LD) [right plot].

4.3.8 Peak Velocity and its position were similar between groups

To ascertain group differences in LD were not related to alterations in peak velocity (PV) and position (y-pos) of PV, PV and y-pos were averaged for each phase (see figure 4.10 and 4.11) and tested for group differences. In experiment 1 ($R^2 = 0.775$) and experiment 2 ($R^2 = 0.763$), PV was not different between the PD and Control group (Exp 1 - *group*: $F(1, 20.0) = 0.275$, $p = 0.606$; *group* × *phase*: $F(3, 60.0) = 2.376$, $p = 0.079$; Exp 2 – *group*: $F(1, 20.0) = 0.194$, $p = 0.664$; *group* × *phase*: $F(3, 60.0) = 0.435$, $p = 0.729$). PV was higher during baseline and washout in both groups and an overall significant effect of *phase* confirmed that PV was not equal across phases; Exp 1: $F(3, 60.0) = 28.605$, $p < 0.001$; Exp 2: $F(3, 60.0) = 36.725$, $p < 0.001$.

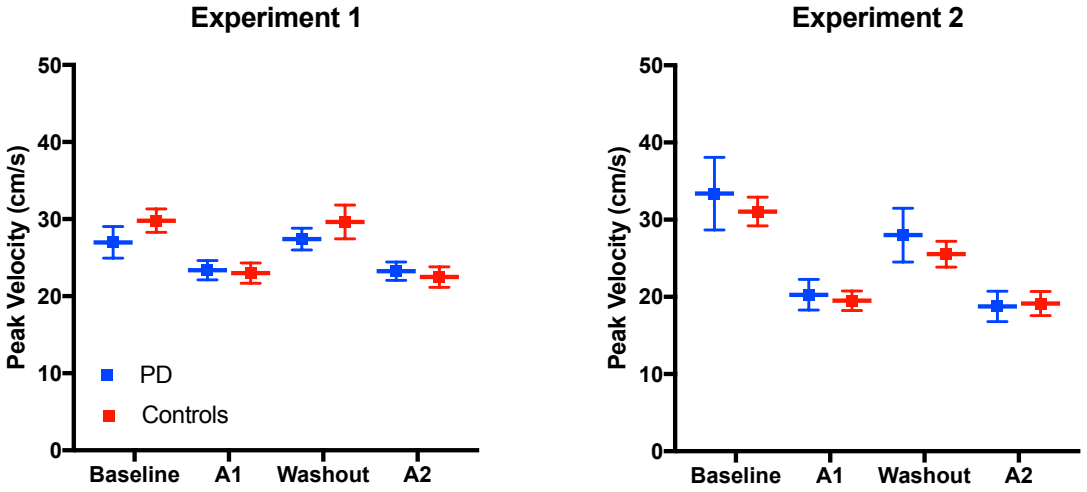


Figure 4.10 Peak velocity (mean + SEM) of the Control (red) and PD group (blue) for the Baseline, Adapt 1 (A1), Washout, and Adapt 2 (A2) phase for Experiment 1 and 2.

For both groups, the y-position of PV was roughly around the middle of the 10 cm reach, see figure 4.11. For experiment 1 ($R^2 = 0.744$) no group differences were found, nor any differences between the phases; *group*: $F(1, 20.0) = 1.547$, $p = 0.228$; *phase*: $F(3, 60.0) = 0.660$, $p = 0.580$; *group* × *phase*: $F(3, 60.0) = 0.091$, $p = 0.965$. No effects for *group* ($F(1, 20.0) = 1.790$, $p = 0.196$) or *phase* ($F(3, 60.0) = 1.070$, $p = 0.369$) were found for experiment 2 ($R^2 = 0.776$). F-tests did show a *group* × *phase* interaction effect; $F(3, 60.0) = 3.029$, $p = 0.036$, but further Bonferroni adjusted post-hoc analysis did not reveal any significant group differences; Baseline: $t(33.1) = 1.599$, $p = 0.119$; Adapt 1: $t(33.1) = 1.665$, $p = 0.105$; Washout: $t(33.1) = 1.394$, $p = 0.173$, Adapt 2: $t(33.1) = -0.081$, $p = 0.936$.

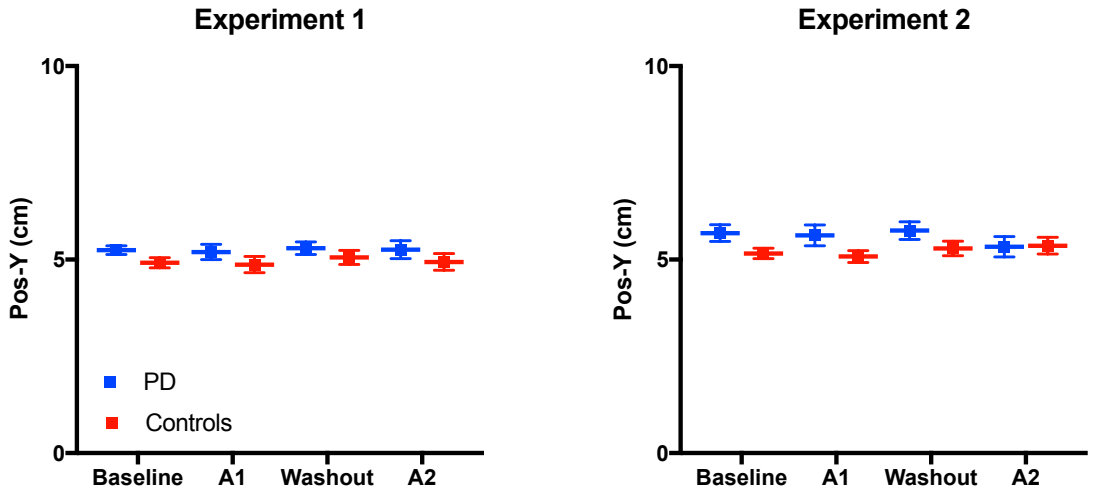


Figure 4.11 Y-position of PV (mean + SEM) shown for Experiment 1 and 2. The y-axis represent the 10 cm reach from start to target. Both the PD (blue) and Control group (red) displayed a PV around the mid-point of the reach.

4.3.9 Explicit awareness of context-force association

In experiment 1, one PD and 1 Control were aware of the relationship between the visuospatial context and the direction of force during the initial adaptation phase. In the Control group 2 participants also gained knowledge of the association at the end of the second adaptation phase. In experiment 2 both the PD and Control group had 4 participants who were aware of the relationship. No clear difference in performance was observed between those who were aware and those we were not.

4.4 Discussion

This study was designed to investigate context-dependent motor adaptation and operant reinforcement in PD. Experiment 1 showed that the PD group maintained a larger error (although only indicated by a trend) compared to Controls both during initial adaptation and re-exposure, which might imply a deficit of contextual motor learning in PD. Force compensation during the initial exposure was largely similar between groups and indicated increased anticipation of the correct force-field after a shift in context had occurred; demonstrating learning in both groups, but force compensation at later stages was reduced in the PD group indicating worse adaptation. Recall of the context-force association was better in Controls, but people with PD also displayed improved adaptation suggesting that although they seemed less able to learn the context-force association a memory was still formed and used upon re-exposure.

In experiment 2 we tried to enhance adaptation by providing additional feedback during the task about the success and failure of the movement, so that the deficit in contextual motor learning of PD participants would become more apparent if they were unable to improve their performance in response to reward and punishment. Some studies have investigated the effects of reward and punishment on motor adaptation in healthy subjects, but so far results are inconclusive. It has been reported that adaptation can be improved using binary monetary punishment (Galea et al. 2015; Song and Smiley-Oyen 2017) or by providing a combination of reward and visual feedback opposed to reward or visual feedback alone (Nikooyan and Ahmed 2015). We chose to strengthen the sense of both reward and punishment by adding auditory feedback to indicate successful and failed

trials, similar as seen in studies on stimulus-response associations (Knowlton, Mangels, and Squire 1996; Ashby et al. 2003), as we were mostly interested in the overall ability of people with PD to modulate their performance in response to enhanced feedback.

Context-dependent adaptation using enhancement feedback revealed a clear divide between the groups. Not only was LD significantly larger in the PD group throughout, force compensation was also reduced compared to Controls. This pattern of results reveals a deficit in learning the context-force association in those affected by PD pathology. In addition to the overall increased LD found in the PD group they failed to show improvements of LD during recall. Results from experiment 2 revealed that Controls showed stronger LD reduction (Exp 1 vs. Exp 2: 0.7 ± 0.2 cm vs. 0.4 ± 0.1 cm [block 60]) in response to the enhanced feedback, possibly caused by a higher activation of operant reinforcement systems. PD participants did not show a similar improvement in response to the enhanced feedback; Exp 1 vs. 2: 1.0 ± 0.1 cm vs. 0.9 ± 0.1 cm [block 60], suggesting reduced sensitivity to reward and/or punishment. However, a direct comparison of data from both experiments did not provide solid evidence that the additional success-based information had a beneficial effect on performance in Controls. It is possible that we failed to find an effect due to low power. Nonetheless, the impairment of context-dependent motor learning as indicated by results from experiment 1 became more apparent in experiment 2 as results revealed a strong deficit in the PD group. It is plausible that reduced sensitivity to feedback about success in PD is contributing to the deficit in context-dependent motor learning.

Success-based feedback was enhanced in Experiment 2, mostly using auditory feedback. However, it must be noted that both experiments included binary information about success, which might have limited the revelation of a reward/punishment feedback effect using direct comparison between experiments. A more pronounced difference between experiments might have been present if success-based feedback was completely absent during experiment 1, i.e. feedback was purely based on visual error rather than also including color-coded information about HIT and MISS trials. It is however questionable if learning the context-dependent motor adaptation would have taken place. While studies show that adaptation is possible using only visual error, studies on S-R associations have shown success-based feedback to be a necessity. We expect performance to deteriorate in both groups if only online feedback would have been provided.

An earlier study by Gutierrez-Garralda et al. (2013) showed that people with PD were unable to adapt to prisms using success-based feedback. Another motor study (Pekny, Izawa, and Shadmehr 2015) showed that a decrease in the probability of reward increased movement variability and that their PD group was impaired at changing movement variability after unrewarded trials, therefore also suggesting altered sensitivity to success-based feedback. Pekny's results actually imply that people with PD were able to modulate their performance using positive but not negative outcomes. However, the level of sensitivity to positive versus negative outcomes might be due to the medication that these patients were on, as Frank et al. (2004) showed that people with PD OFF medication were more sensitive to negative than positive outcomes and that medication

reversed this phenomenon, i.e. PDs ON medication had increased sensitivity to positive but not negative outcomes. If the medication-dependent sensitivity as shown by Frank also applies to our study, our PD groups, who were ON medication, should display more sensitivity to positive than negative feedback.

An interesting observation was that both the PD and Control group of experiment 2 showed retention of LD, while these aftereffects were absent in experiment 1. It has been shown before that providing a stronger reward during learning (Galea et al. 2015; Abe et al. 2011; Song and Smiley-Oyen 2017) or removing visual error completely and making participants purely rely on success-based information (Shmuelof et al. 2012) improves retention of a visuomotor adaptation. Although we can only speculate about the exact contributions of reward and punishment on our task, it is plausible that the beneficial effect on retention was caused by augmentation of reward. And subsequently, that punishment enhanced adaptation itself, similar to Galea et al. (2015). Even though the PD group performed worse compared to Controls their LD still fell on average within the 2 cm boundary (see figure 4.2 and 4.4), so despite worse performance they were still rewarded on a large part of trials which can also be seen from the analysis of the MISS trials; during Adapt 1 ~25% of trials were MISS trials for the PD group. The presence of aftereffects in PD could suggest increased sensitivity to reward similar as proposed by Frank's study.

Following from these points would lead the conclusion that if we had tested PD participants OFF medication, retention could have been absent (while context-dependent adaptation itself could have been relatively preserved compared to Controls instead).

With respect to our task, this theory would only apply if negative feedback would mostly be driving the acquisition of the context-dependent force-field adaptation, similar as seen for regular VMR or force-field tasks, while reward would maintain the association. Instead, it seems more plausible that acquisition of the context-force relationship itself is driven both by reward and punishment; negative feedback driving adaptation to each force-field, while rewarding feedback linking a decline in error to the correct context leading to improved performance, i.e. both reward and punishment feedback are necessary to achieve overall adaptation / learn the task. Shohamy et al. (2005) showed that PDs OFF medication were more impaired at learning S-R associations compared to those ON medication, showing that learning S-R associations might largely rely on positive feedback. While testing PDs OFF medication on our context-dependent motor task could make them more sensitive to negative feedback driven adaptation to each force-field, it would presumable lead them to be less sensitive to rewarding feedback which drives the formation of the context-force association. Investigating the separate effects of reward and punishment on context-dependent force-field adaptation would help establish the separate contributions of reward and punishment on the acquisition of the context-dependent task and its retention.

Earlier studies have shown motor memory, as tested by savings, to be affected in PD (Marinelli et al. 2009; Bédard and Sanes 2011; Leow, Loftus, and Hammond 2012). Some of our measures indicated a weaker motor memory in PD compared to Controls, but their performance did not seem to be naïve upon re-exposure to the context-dependent force-field. Especially FC-values of Adapt 2 indicated improved anticipation of the

correct field as FC was positive (Exp 1) or rapidly turned positive (Exp 2) in comparison to Adapt 1 where FC was more negative at the start of adaptation. Based on the FC, it seemed that PD participants largely maintained what they had learned during the initial adaptation phase as they returned more rapidly to values reached at the end of the first adaptation, therefore suggesting relatively preserved motor memory. These findings are in line with results from the previous chapter, which showed savings of force-field adaptation to be intact in PD.

In our previous study (Chapter 3) we suggested that interference might have been diminished in PD because of a weaker link between the adapted state and the associated context. In our present task it was impossible to acquire the two adapted states without taking in account the contexts. With this task we showed that indeed people with PD were less able to develop context-motor associations, but that the associations that they make are preserved to some extent. Our results therefore show that the habitual and procedural learning problems in PD as shown by cognitive behavioural studies (Saint-cyr, Taylor, and Lang 1988; Knowlton, Mangels, and Squire 1996; Ashby et al. 2003) also apply to motor behaviour. Moreover, Experiment 2 implies that learning the context-force associations largely relies on feedback about success (rather than error) and that insensitivity to this feedback presumably underlies the weaker context-force associations in PD. This result is in line with studies showing that the deficits in procedural learning in PD are caused by impaired operant reinforcement mechanisms, which are modulated by dopamine (Frank 2004; Shohamy 2005).

However, while the role of dopamine remains contentious, it is clear that dopamine does not signal reward per se, but something akin to a reward-prediction error (RPE) (Schultz 2016) – i.e. whether or not the reward matches the expected reward. Peaks in dopamine release often occur when reward is higher than expected, while dips are often seen when reward is lower than expected (Schultz, 2002). Due to the depletion of dopamine in PD, dopamine spikes are thought to be muted (Frank et al. 2004) leading to a weaker RPE response. Interestingly, Nakahara et al. (2004) showed that dopamine neurons in the midbrain not only represent RPE, but that this RPE is also context-dependent. Their results imply that the RPE can predict dopamine release more faithfully when context is taken into account, but only when that context is relevant to the behavioral outcome. Altogether, it seems plausible that motor states are mostly reinforced in relation to contextual cues present during learning, a process that seems to be weaker in PD. If the relevance of the context can also influence formation and/or retrieval of the motor state than this may explain why various task conditions yield different results in PD.

In conclusion, we showed that two opposing force-fields can be learned simultaneously when each field is linked to a distinctive context. In addition, we showed that learning the context-force association improved in Controls when feedback about success and failure was strengthened using additional reward and punishment. More importantly, our results showed a deficit of context-dependent motor adaptation in PD, which was presumably caused by altered sensitivity to reward and punishment.

Chapter 5

The effect of Reward and Punishment on Contextual Motor Adaptation in Young Adults

5.1 Introduction

In our previous study (Chapter 4) we investigated context-dependent force-field adaptation and operant reinforcement in people with PD and older Controls and found a stronger difference between groups by providing additional reward and punishment feedback. Processes involved in learning the context-force associations as well as reinforcement of the contextual-motor states seemed activated to a higher degree in Controls by the addition of auditory feedback. In the PD group we observed an ability to learn and retain the context-dependent motor adaptation to some extent, but improved learning in response to enhancement of reward and punishment was reduced. However, while the PD group showed no added benefit of enhanced feedback on contextual motor learning itself, they did display increased retention implying that their behaviour was still sensitive to certain aspects of the augmented reward and punishment feedback.

People with PD have no major cerebellar pathology and learning driven by cerebellar mechanisms has been shown to be largely intact (Marinelli et al. 2009; Bédard and Sanes 2011; Leow, Loftus, and Hammond 2012; Leow et al. 2013), but the BG pathology is the hallmark of PD and behaviour driven by the BG is known to be affected (Saint-cyr, Taylor, and Lang 1988; Knowlton, Mangels, and Squire 1996; Shohamy et al. 2004). Motor adaptation is a cerebellar-dependent process driven by the sensory prediction error (SPE); an error representing the difference between the expected and observed sensory error. The BG on the other hand is thought to operate through a reward-prediction error (RPE), which is modulated by dopamine. Peaks in dopamine indicate that an obtained reward is higher than expected, while dips of dopamine specify a reward

being lower than expected (Schultz, Dayan, and Montague 1997). Although we can only speculate about the processes involved in driving contextual motor learning we presume that it involves both reward-based learning, which is thought to rely on the BG, and motor adaptation, a cerebellar-dependent process.

Recent studies have investigated the effects of reward and punishment on motor adaptation. Shmuelof et al. (2012) showed that binary information of success or failure during a VMR task led to enhanced retention in the absence of visual error signals. A similar improvement in retention was shown by Galea et al. (2015), using monetary reward, but in contrast to Shmuelof's study visual error was present during the adaptation phase and only absent when retention was measured. Interestingly, Galea's (2015) study revealed that when negative binary monetary feedback was given an increased adaptation rate was observed instead, therefore showing a dissociative effect of reward and punishment on adaptation and retention. The differential effects of reward and punishment were replicated by Song & Smiley-Oyen (2017) in an experiment that manipulated the distribution of positive and negative feedback probability. Nikooyan & Ahmed (2015) also found some evidence that retention was improved in those only receiving reward feedback, but their main finding was that a combination of reward and visual feedback accelerated adaptation compared to those only receiving reward or visual feedback. Van der Kooij and Overvliet (2016) on the other hand showed that adaptation was not possible when only reward, and not spatial error, was provided. Though no adaption was seen with only reward feedback, they found differences in adaptation groups receiving only spatial error or a combination of spatial error and reward. Altogether it

remains unclear how reward and punishment exactly affect adaptation and retention and what their influence is in combination with visual error signals.

Reward and punishment have shown to have a differential effect on other forms of procedural learning. Wächter et al. (2009) showed that reward, but not punishment, improved learning of a serial reaction time (SRT) task. They also found a strong performance effect of punishment, where reaction times dropped when sequences were random, which could indicate that overall motor performance improved due to a motivational component triggered by negative feedback. An overall non-sequence specific improvement of learning in the punishment group was also found by Steel et al. (2016). In addition, they showed that both reward and punishment had a beneficial effect only on early learning of the SRT sequence. No effect of feedback was found on retention of the learned sequences.

By investigating the separate effects of reward and punishment on contextual motor learning we hope to better our understanding about the processes involved and the deficits that people with PD display. In this study we investigated the effect of reward and punishment on context-dependent force-field adaptation in healthy young adults using the context-dependent motor task as explained in Chapter 4. All participants were exposed to a randomly alternating force-field, which could be learned using the field-specific context provided, and subsequently tested for recall. To investigate the separate and additional effect of reward and punishment participants were divided in 4 groups. In the Control group success and failure was indicated by a change in colour of the target. Those in the Punishment-group received additional auditory feedback for failed trials,

while the Reward-group got auditory and visual feedback for successive trials instead. The latter group received all forms of feedback.

5.2 Materials and Methods

5.2.1 Participants

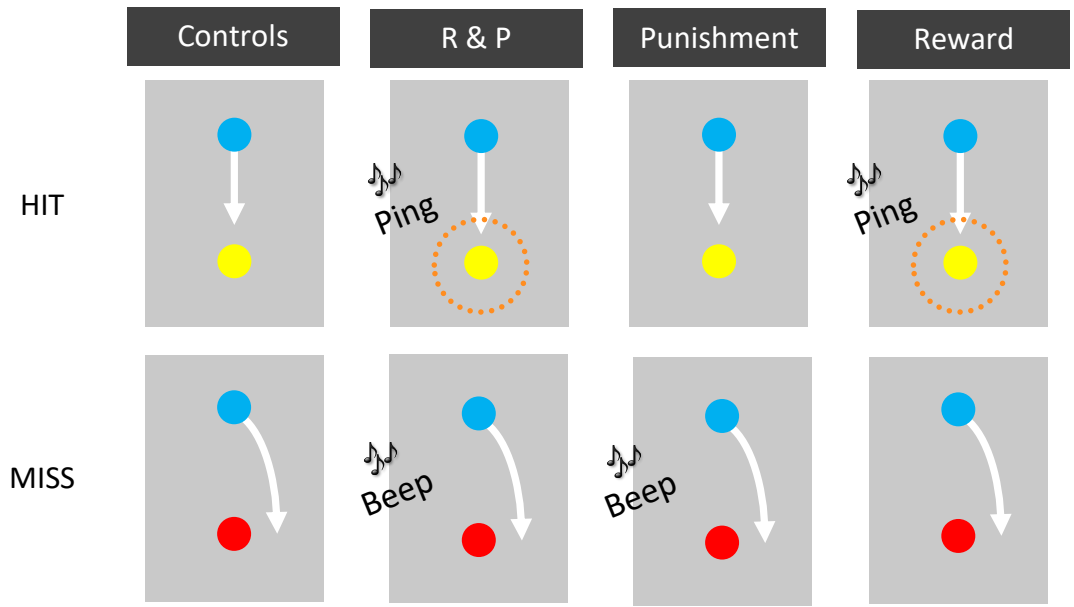
Forty-eight healthy young participants (Age range: 18 - 43) were included in this study and pseudo-randomly assigned to one of 4 groups; Controls (N = 12, 8 females, Age 23 ± 1), R&P (Reward & Punishment, i.e. enhanced feedback; N = 12, 7 females, Age 22 ± 1, 1 left-handed), Punishment-group (N = 12, 8 females, Age 22 ± 1), and Reward-group (N = 12, 8 females, Age 22 ± 2, 1 left-handed). Age ($F(3, 44) = 0.028$, $p = 0.994$), gender ($\chi^2(df = 3, N = 48) = 0.273$, $p = 0.965$), and handedness ($\chi^2(df = 3, N = 48) = 2.087$, $p = 0.555$) were not different between the groups. Protocols involved in the study were approved by the University of Birmingham ethical committee and all participants gave their written informed consent prior to partaking in the study.

5.2.2 Experimental set-up

The task used in this study was similar to the task described in Chapter 4. In summary, participants performed 200 trials of baseline and 400 trials of adaptation (Adapt 1). Then a 30-minute break followed, after which participants performed another 200 trials of washout and 400 trials of adaptation (Adapt 2). The feedback received by the Control and R&P-group corresponds to experiment 1 and experiment 2 of Chapter 4, respectively. Accordingly, for the Control group a HIT and MISS were indicated by a change in colour of the target (yellow for HIT, red for MISS), while the R&P group received additional feedback (auditory + visual explosion). The Punishment-group received auditory

feedback (a buzzer) during failed trials (trials on which the target was missed or movements went outside the ±2 cm window) in addition to the limited feedback (red target). During correct trials the target turned yellow, but no sound was played. The Reward-group got enhanced feedback (pleasant sound + visual explosion) during correct trials instead plus a yellow target and normal feedback (red target) when a trial was unsuccessfully executed, see Table 5.1. After the break all groups received feedback similar to Controls; success and failure only indicated by colour. Visuospatial context and direction of force were counterbalanced within each group so that half of the participants experienced the CW field during a left shift and the CCW field during a right shift, while the other half experienced a CCW for left and a CW field for right. Participants were not told about the relationship between the context and direction of the force-field and were asked about their explicit knowledge after completion of the task.

Table 5.1. Feedback after HIT and MISS trials as received during Baseline and Adapt 1. During Washout and Adapt 2 all groups received feedback as shown for Controls.



5.2.3 Data and Statistical Analysis

LD and FC were the main measures of performance and were calculated, sign adjusted, and averaged in blocks using MATLAB (The MathWorks, Version R2016b) as described in Chapter 4. Prior to averaging in blocks outliers were identified, which led to the removal of 3-4% of LD trials (Controls: 3.2% (1.7% miss trials; 1.5% hit trials), R&P: 4.2% (2.0% miss; 2.2% hit), Punishment: 3.9% (2.0% miss, 2.0% hit), Reward: 3.9% (2.0% miss, 1.9% hit)) and the removal of 2-5% of FC trials (Controls: 2.5% (0.1% miss trials, 2.4% hit trials), R&P (3.8% (0.1% miss, 3.8% hit), Punishment: 4.7% (all hit), Reward: 3.9% (all hit)). Statistical analysis was also largely similar to Chapter 4. Group differences in adaptation were tested using an LME model in RStudio (R Core Team 2016) and included fixed effects *group* (Controls, R&P, Punishment, and Reward), *phase* (Adapt 1 vs Adapt 2), and *block* (LD: blocks 21 – 60 [Adapt 1], and blocks 81- 120 [Adapt 2], or FC: blocks 11 – 30 [Adapt 1], and blocks 41 – 60 [Adapt 2]), and *subject* as random effect, according to:

$$DV \sim group \times phase \times polynomial(block, 2) + (phase \times polynomial(block, 2) \mid subject) \quad \text{[eq. 5.1]}$$

DV being the dependent variable, which was either the LD or FC data. Differences in baseline, washout and retention were also assessed as outlined in Chapter 4.

Other measures (repeat-switch patterns, percentage MISS trials, and peak velocity (PV)) were tested for group differences using a mixed model including fixed effects *group* and *sequence*/*phase,* and *subject* as random effect.

5.3 Results

5.3.1 Lateral Deviation was not different between groups

All groups adapted to the context-dependent force-fields and showed improved performance during re-adaptation. There were slight differences in adaptation between the groups, but no statistical group differences were found.

The task began with a baseline phase during which participants were exposed to the visuospatial shifts, i.e. the context, while forces of the robot were turned off. All groups experienced the feedback as displayed in table 5.1, which let to no obvious differences in baseline performance as seen in figure 5.1. Hereafter, outwards reaching movements were perturbed by a force-field (CW or CCW) in relation to the visuospatial shift as outlined in the method section. Groups continued to experience feedback in association with table 5.1. At the start of the initial adaptation (block 21) LD increased in all groups and was lowest in the Punishment-group; Controls: 1.5 ± 0.1 cm, R&P: 1.3 ± 0.1 cm, Punishment: 1.2 ± 0.1 cm, Reward: 1.7 ± 0.1 cm. All groups showed consistent reduction of LD during Adapt 1, although the decline seemed the strongest in the Punishment-group (0.4 ± 0.2 cm [block 60 – end of Adapt 1]), weakest in the Control-group (0.9 ± 0.1 cm), and similar in the R&P (0.5 ± 0.1 cm) and Reward-group (0.6 ± 0.1 cm). After the 30-minute break that followed participants firstly performed a de-adaptation phase (discussed below) that drove LD back to baseline-levels. At this point feedback in all groups was the same; only colour-coded feedback was provided.

The end of baseline and end washout (average last two blocks: 19-20 vs. 79-80) were assessed for group differences ($R^2 = 0.689$), which showed no overall main effect of *group*; $F(3, 48.0) = 0.290$, $p = 0.832$, nor a *group* × *phase* interaction effect; $F(3, 48.0) = 1.371$, $p = 0.263$, indicating that the end of baseline and end of washout equal was between groups. There was an overall effect of *phase* (all groups taken together); $F(1, 48.0) = 16.412$, $p < 0.001$, suggesting that LD was not completely back to baseline levels at the end of de-adaptation in all groups, which can also be seen in figure 5.1.

After the washout phase participants performed the adaptation phase for the second time. LD at the start of Adapt 2 increased, but was lower in comparison to the initial adaptation; Controls: 1.1 ± 0.1 cm, R&P: 1.0 ± 0.1 cm, Punishment: 1.1 ± 0.1 cm, and Reward: 1.2 ± 0.1 cm, and declined more rapidly. LD at the end of Adapt 2 was again lowest in the Punishment-group (0.1 ± 0.2 cm), similar in the Control and R&P group (0.6 ± 0.1 cm for both), and 0.4 ± 0.1 cm in the Reward-group. Although the numerical values indicated some differences between the groups statistical tests on the LME model of adaptation ($R^2 = 0.772$) did not reveal a significant main effect of *group*, $F(3, 48.0) = 0.996$, $p = 0.403$, or *group* × *phase* (Adapt 1 vs Adapt 2) interaction effect, $F(3, 48.0) = 0.434$, $p = 0.723$, meaning that the initial and secondary adaptation similar was between groups. A main effect of *phase* ($F(1,48.0) = 123.877$, $p < 0.001$) and *phase* × *block* effect ($F(2, 48.0) = 27.062$, $p < 0.001$) were found, confirming that both the intercept and learning curve of LD were improved during Adapt 2 in all groups. Altogether, these results indicate the presence of savings after contextual motor adaptation. For individual trajectories see Figure S5 (Appendix I).

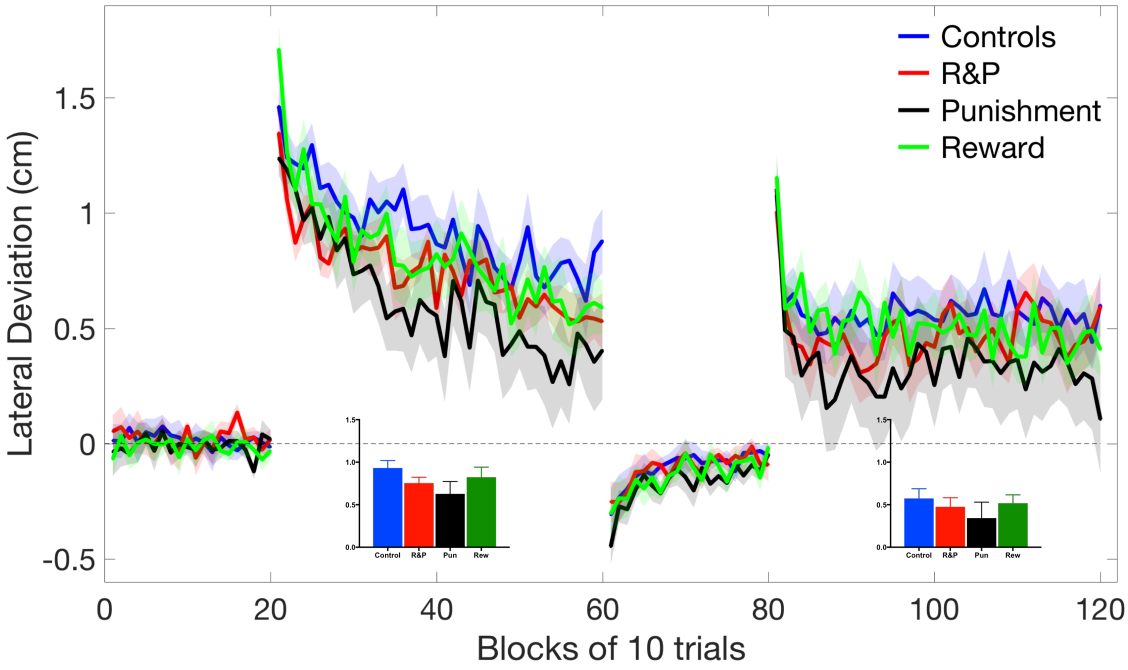


Figure 5.1 Lateral deviation shown for Baseline (block 1 – 20), Adapt 1 (block 21 – 60), Washout (block 61 – 80), and Adapt 2 (block 81 – 120) for Controls (blue), R&P (red), Punishment (black), and the Reward group (green). A 30-minute break took place between Adapt 1 and the Washout phase. Bar graphs indicate the mean LD (±SEM) for Adapt 1 and Adapt 2.

5.3.2 Feedback had no effect on Force Compensation

Force compensation was successfully increased by all groups during adaptation and performance improved during re-adaptation. Overall, no group differences were found.

FC was calculated from the error-clamp trials that were interspersed among the normal trials and positioned after a change in context occurred, never after a repetition of the same context. No forces were imposed during baseline and as expected FC was around zero for all groups, see figure 5.2. At the start of Adapt 1 participants showed a negative

FC, which was lowest in Controls; -31.9 ± 6.8 % [block 11 – start of Adapt 1], and -15.0 ± 7.9 %, -22.3 ± 8.4 %, and -18.7 ± 6.7 % , in the R&P, Punishment, and Reward-group, respectively. The negative FC indicates that participants were pushing in the opposite direction as desired, i.e. they were responding to the force prior to the switch in context. Over time all groups learned to increase their FC, but this adaptation seemed slightly better in the Punishment and Reward-group. At the end of the initial adaptation FC was 43.1 ± 10.3 % in Controls, 47.9 ± 10.8 % in R&P, 54.9 ± 11.3 % in the Punishment, and 48.0 ± 8.7 % in the Reward-group [block 30].

After the 30-minute break the washout-phase showed some retention in the groups (discussed below) and FC values comparable to baseline at the end of de-adaptation. Statistical tests ($R^2 = 0.533$) on the end of baseline (average block 9 – 10) and washout (average block 39 – 40) did not reveal any group differences; *group* $F(3, 48.0) = 0.300$, $p = 0.825$, and *group* × *phase* $F(3, 48.0) = 1.051$, $p = 0.379$. Hence, all groups started adaptation and re-adaptation from a similar level. However, similar to LD de-adaptation seemed not complete (in all groups) as an overall effect was found for *phase* (baseline vs. washout); $F(1, 48.0) = 9.215$, $p = 0.004$. Re-adaptation started with positive FC values for all groups; Controls 26.8 ± 6.1 %, R&P 11.1 ± 8.0 %, Punishment 23.7 ± 9.6 %, and Reward 16.2 ± 4.0 % [block 41], indicating improved performance. FC was variable in all groups, although the Punishment-group seemed to perform best, see bar graph Adapt 2. The second adaptation was ended with an FC of 38.8 ± 12.0 % in Controls, 45.6 ± 7.9 % in R&Ps, 62.8 ± 9.7 % in the Punishment-group, and 41.9 ± 12.1 % in the Reward-group [block 60].

F-tests on the LME model of FC ($R^2 = 0.613$) were similar to results from the LD. No main effect of *group*: $F(3,48.0) = 1.109$, $p = 0.355$, or *group* × *phase*: $F(3, 49.1) = 0.762$, $p = 0.521$, was found, showing that despite slight differences adaptation and re-adaptation were similar between the groups. The improvements in FC during re-adaptation shown by all groups were confirmed by a main effect of *phase;* $F(1, 49.1) = 57.645$, $p < 0.001$, and *phase* × *block* interaction; $F(2, 51.6) = 34.169$, $p < 0.001$, meaning that both the intercept and curve of adaptation were improved. In summary, differences in feedback had no effect on context-dependent motor adaptation and recall in young adults.

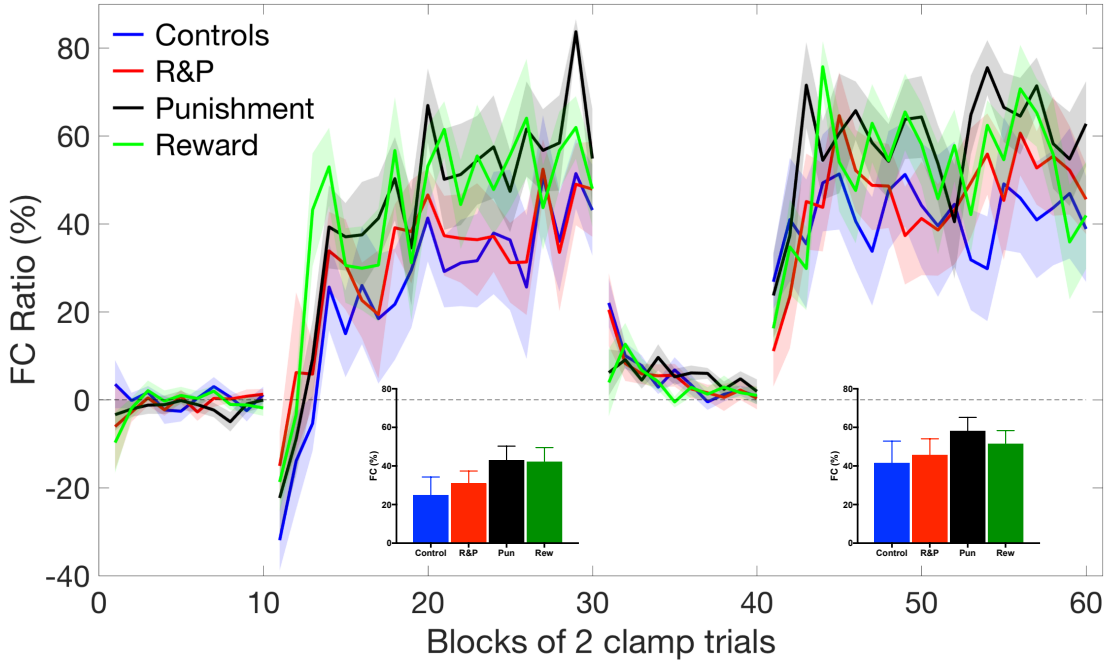


Figure 5.2 Group average of force compensation (in percentage) shown for Baseline (block 1 – 10), Adapt 1 (block 11 – 30), Washout (block 31 – 40), and Adapt 2 (block 41 – 60). A 30-minute break took place between Adapt 1 and the Washout phase. A negative FC indicates compensation in the opposite direction as required. Bar graphs display mean FC (± SEM) for Adapt 1 and Adapt 2.

5.3.3. Observed Power

Despite slight differences in performance no significant group differences were found, which might be caused by low power. In R using the powerSim-function from the simr-package the observed power for the fixed effect *group* was calculated for the LD and FC data at $\alpha = 0.05$. Due to the complex nature of the statistical model the observed power was determined by comparing the LME model (including the fixed effect *group*) to a model without the fixed effect *group*; the power analysis was done using the fcompare-function and therefore no effect size was reported. For LD an observed power of 89.00% (81.17 - 94.38 [95% confidence interval]) was determined. FC showed an observed power of 84.00% (75.32 - 90.57 [95% CI]). These results indicate that low power is unlikely causing the absence of statistical group differences.

5.3.4 Retention was present and slightly variable between the groups, but overall unlearning was similar

Both for the LD and FC some retention of the initial adaptation was present after the 30-minute break as can be seen in figure 5.1 (LD: block 60 – 80) and figure 5.2 (FC: block 30 – 40). The LD at the start of unlearning (block 61) was highest in the Punishment-group; -0.4 ± 0.1 cm, but very comparable to the -0.3 ± 0.1 cm deviation that the other groups showed. Remarkable was that the Control and R&P group showed substantially larger FC (22.0 ± 5.5 % and 20.5 ± 8.3 %, respectively) at the start of de-adaptation (block 31) compared to the Punishment and Reward-group (6.2 ± 5.3 % and 3.9 ± 7.7 %, respectively).

To investigate differences in de-adaptation between the groups the whole washout phase was fit with an LME model (LD: $R^2 = 0.643$; and FC: $R^2 = 0.643$), which did not reveal a main effect of *group* for LD ($F(3, 48.0) = 0.537$, $p = 0.659$) or FC ($F(3, 48.0) = 0.252$, $p = 0.860$), nor a *group* × *block* effect (LD: $F(6, 86.9) = 0.321$, $p = 0.925$; FC: $F(6, 84.0) = 1.273$, $p = 0.279$), therefore confirming that de-adaptation similar was between the groups. However, a main effect for *block* was found (LD: $F(2, 87.0) = 22.443$, $p < 0.001$; FC: $F(2, 84.0) = 12.904$, $p < 0.001$), indicating that all groups showed significant unlearning.

5.3.5 Feedback did not alter repeat-switch response patterns

The repeat-switch patterns of the four groups showed a similar divide as seen for the adaptation itself. However, statistical tests on the repeat-switch patterns (i: $R^2 = 0.842$; ii: $R^2 = 0.839$; iii: $R^2 = 0.858$; iv: $R^2 = 0.937$) did not reveal any *group* differences (i: $F(3, 48) = 0.996$, $p = 0.403$; ii: $F(3, 48.0) = 1.193$, $p = 0.322$; iii: $F(3, 48) = 0.936$, $p = 0.431$; iv: $F(3, 48) = 0.955$, $p = 0.422$) or *group* × *sequence* interaction effects (i: $F(9, 144) = 0.567$, $p = 0.822$; ii: $F(9, 144) = 0.893$, $p = 0.534$; iii: $F(9, 144) = 0.661$, $p = 0.743$; iv: $F(9, 144) = 0.315$, $p = 0.969$). These results therefore show that altered feedback does not lead to differences in repeat-switch response patterns in young adults.

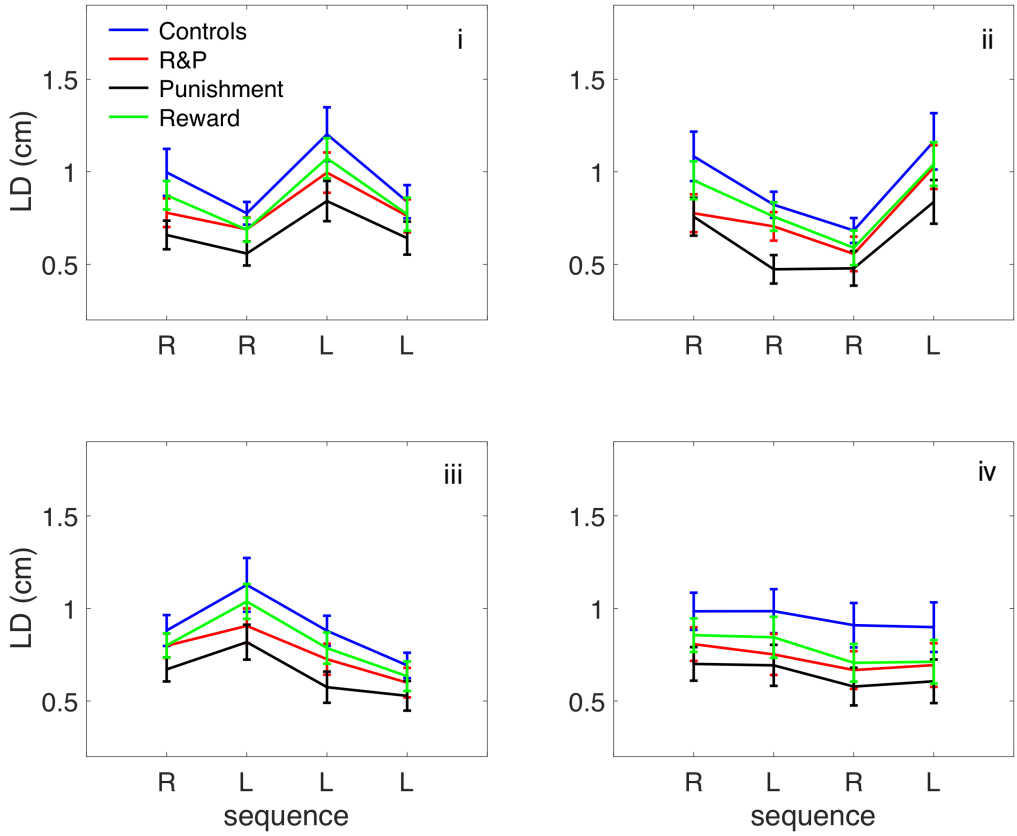


Figure 5.3 Repeat-switch response patterns shown for Controls (blue), R&P (red), Punishment (black), and Reward (green) group. LD was averaged over 4 different sequences (I – iv) and displayed as the mean + SEM.

5.3.6 Percentage of MISS trials was not different between groups

For all groups the percentage of MISS trials was highest during the first adaptation phase, see figure 5.4, where the Control group showed the largest amount of MISS trials. During Adapt 2 the percentage of MISS trials was reduced. All groups showed near zero MISS trials during the baseline and washout phase. The different forms of feedback did not have an effect on the percentage of MISS trials ($R^2 = 0.757$) during baseline, Adapt 1, washout, and Adapt 2 as no main effect of *group*; $F(3, 48.0) = 0.103$, $p = 0.958$, and *group* × *phase*;

F(9, 144.0) = 0.459, p = 0.900, was found. A main effect of *phase*; F(3, 144.0) = 171.7, p < 0.001, was shown.

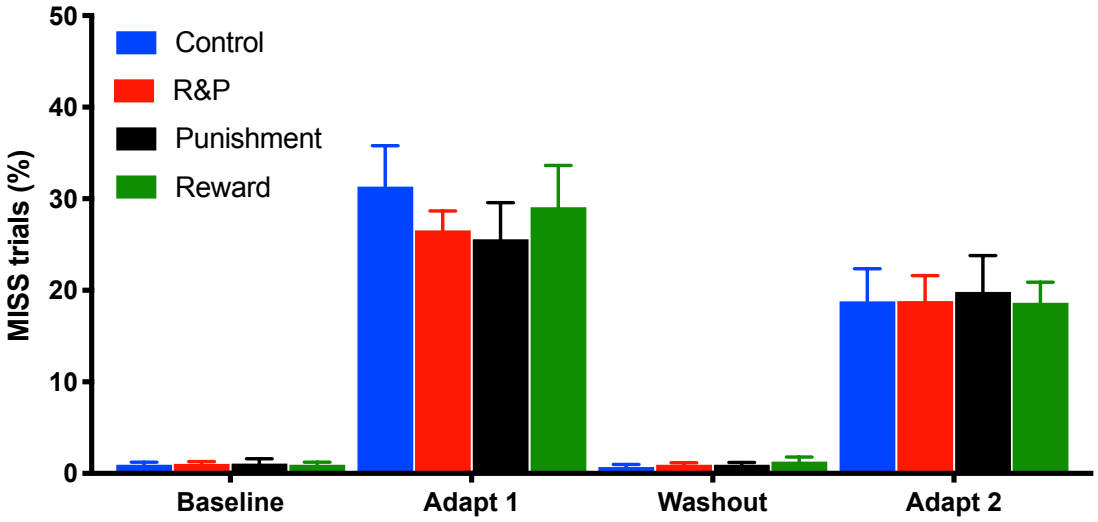


Figure 5.4 Percentage of MISS trials (mean ± SEM) for Baseline, Adapt 1, Washout and Adapt 2 for Controls (blue), R&P-group (red), Punishment-group (black), and Reward-group (green).

Further analysis showed that the MISS trials were mostly due to participants exceeding the ±2 cm boundary from the midline, rather than failing to land in the target, see figure 5.5. Exceeding the 2cm-boundary was dependent on the maximum LD (Max LD) for every trial. Figure 5.6 shows that Max LD was significantly correlated with the LD at PV; r = 0.87, p < 0.001. Only a small part of MISS trials were due to missing the target. End accuracy as measured with end LD (LD at the level of the target) was also correlated with LD at PV; r = 0.17, p < 0.001. Altogether, these results show that both Max LD and End LD, of which mainly the former forms a fundamental aspect of whether you were rewarded or punished, link to LD at PV (displayed in figure 5.1).

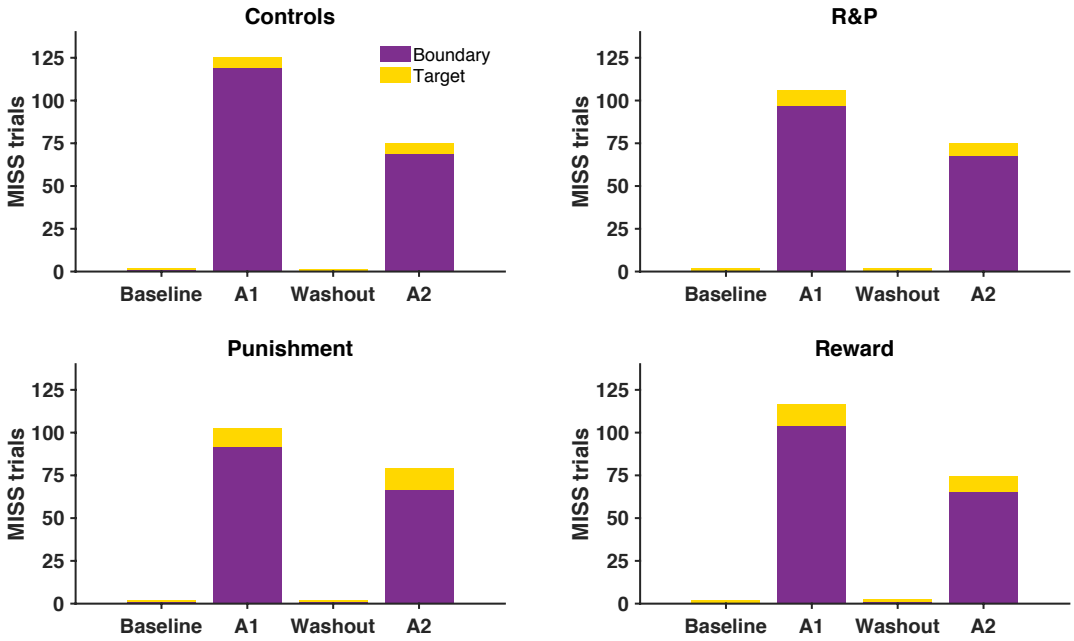


Figure 5.5. Number of MISS trials due to exceeding the 2cm-boundary (purple) or missing the target (yellow) for Controls (top left), the R&P group (top right), the Punishment group (bottom left), and the Reward group (bottom right), separately shown for Baseline, Adapt 1 (A1), Washout phase, and Adapt 2 (A2).

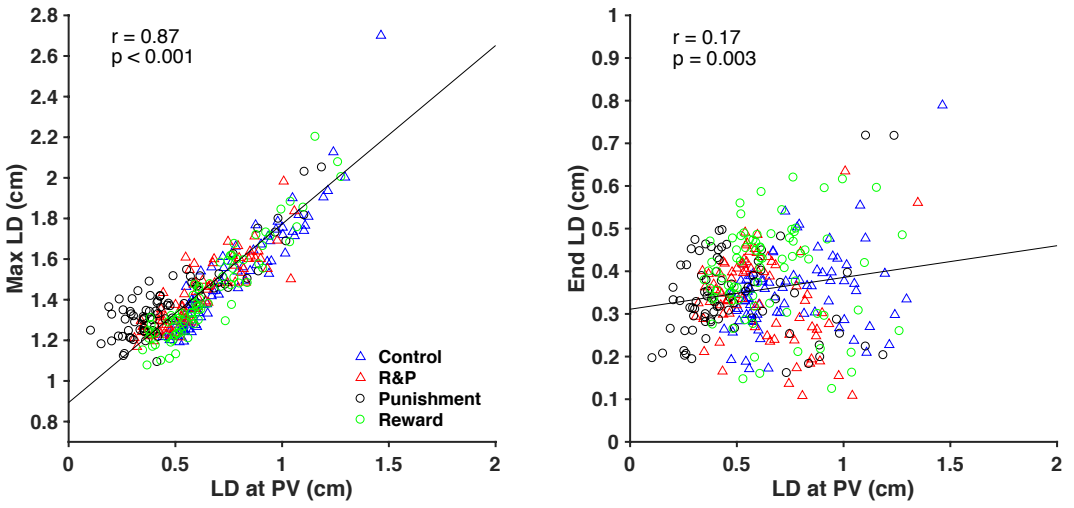


Figure 5.6 Correlation plots of the LD at peak velocity (LD at PV) and the maximum LD (max LD) [left plot] and the LD at PV and the end accuracy (end LD) [right plot].

5.3.7 Peak Velocity during baseline and re-adaptation was different between the groups

Figure 5.7 shows the group average of peak velocity at the different phases of adaptation. Statistics on PV ($R^2 = 0.732$) revealed a significant effect of *phase*, $F(3, 144.0) = 53.643$, $p < 0.001$, and *group* × *phase*, $F(9, 144.0) = 4.188$, $p < 0.001$, and a trend for *group*, $F(3, 47.997) = 2.682$, $p = 0.057$. Post-hoc tests, for each phase separately, showed that peak velocity was significantly different between Controls and the R&P-group during baseline, $t(103.3) = -3.188$, $p = 0.011$, and between Controls and the Punishment-group during re-adaptation, $t(103.3) = -3.052$, $p = 0.017$. There was also a difference between the R&P and Punishment-group during re-adaptation, $t(103.3) = -3.409$, $p = 0.006$. No further group differences were found.

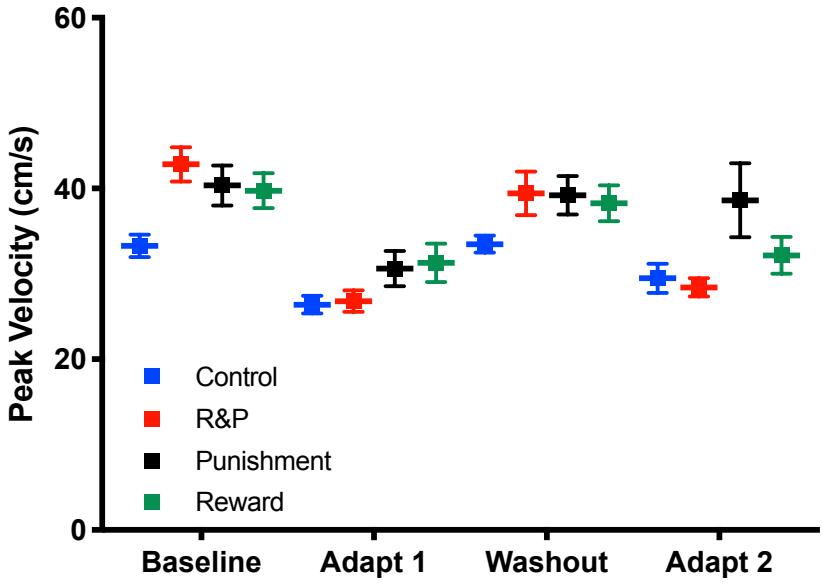


Figure 5.7 Peak velocity (mean + SEM) for the Baseline, Adapt 1, Washout, and Adapt 2 phase for Controls (blue), R&P-group (red), Punishment-group (black), and Reward-group (green).

5.3.8 Explicit knowledge of context-force association

In total, 29 out of the 48 participants (60%) claimed to be aware of the link between context and force and they were roughly equally divided among the four groups; in the Control group 7 were aware, in the R&P and Punishment group 8 participants developed explicit knowledge about the relationship between context and direction of force, and in the Reward-group there were 6 aware.

5.4 Discussion

This study was set up to investigate how reward and punishment influence context-dependent force-field adaptation in young healthy adults. All feedback groups showed adaptation, retention, and improved performance during secondary adaptation. Adaptation was lowest in the Control group, who did not receive any additional feedback for successful or failed trials, and fastest in the Punishment-group (the repeat-switch response patterns revealed a similar divide between the groups), but the LD and FC results were inconclusive as no group effects were found.

Overall our results imply that participants who received augmented punishment performed slightly better on the contextual motor task, which would be in line with earlier research showing that punishment can have a beneficial effect on the reduction of error during adaptation (Galea et al. 2015; Song and Smiley-Oyen 2017). SRT tasks have also shown improved motor performance in those receiving punishment, but this was claimed to be a non-learning effect possibly stemming from increased motivational incentives (Wächter et al. 2009; Steel et al. 2016). Whether improvements caused by punishment are due to increased motivation or whether the feedback acts directly on learning mechanisms is uncertain. In addition, the effects of punishment (and reward) could be task specific. Punishment during a pinch force task – a task where error could be reduced by modulating force production - did not lead to improved performance (Abe et al. 2011), and another study, which used a similar task; a force tracking task, even showed impaired performance in response to punishment (Steel et al. 2016).

Assessment of peak velocities illustrated increased speed during baseline in all three groups receiving additional feedback compared to Controls (significant in R&P vs. Control group), which demonstrates that adding feedback about success, whether reward or punishment, invigorates movement, possibly indicating increased motivation. It was shown before (Muhammed et al. 2018) that individual levels of motivation influenced the ability to modulate the velocity of saccades and that monetary rewards and losses influenced peak velocity further, which could indicate that reward and punishment influence intrinsic motivation. Our results showed that during initial adaptation peak velocities were comparable between the groups, therefore suggesting that (motivational) benefits from the additional feedback, such as shown during baseline, did not hold when task difficulty increased. Interestingly though, during re-adaptation, when additional feedback conditions were removed and all groups received the same feedback, i.e. feedback as Controls, the Punishment-group displayed a higher PV compared to Controls and the R&P-group, which could indicate that Punishment had a lasting effect on movement speed.

No profound differences were found on retention. Our results are therefore in contrast to earlier studies, which showed that reward had a beneficial effect on retention (Shmuelof et al. 2012; Galea et al. 2015; Song and Smiley-Oyen 2017). Importantly though, this effect was only found when vision of error was removed. The latter two studies showed that when visual error was present – as during our study – no group differences were found on retention, which could therefore explain why we do not see a similar effect. Earlier research has also shown that an acquired adapted state decays more

quickly when online visual feedback is provided opposed to feedback about the distance but not direction of movement (Lago-Rodriguez and Miall 2016). The idea is that the lack of visual error engages the reinforcement-based learning processes to a higher degree slowing down decay. The presence of visual error during our task could have possibly limited the effect of reward-based reinforcement mechanisms therefore not revealing any group differences.

In addition, it must be noted that our Control group still received binary information about trial success, i.e. HIT and MISS trials were indicated by a change in colour of the target. The additional punishing (auditory) and rewarding feedback (auditory + visual explosion) as used by the other conditions might not have been sufficient enough to distinguish the involved reward-based processes from those involved during the Control condition, therefore failing to show clear behavioural changes. Comparison of the enhanced feedback conditions to a group where learning the context-dependent task was purely reliant on visual error might have ameliorated the effects as shown by the current results.

Results from Chapter 4 showed that augmentation of reward and punishment improved LD reduction in healthy older adults. Figure 5.1 shows a small reduction of LD in the R&P-group compared to the Control group, which might indicate a similar effect of augmented reward and punishment on younger adults. Generally, older adults have shown to perform worse on a motor adaptation task compared to younger adults (Panouillères et al. 2015; Hardwick and Celnik 2014), and display reduced sensitivity to reward on cognitive tasks (Mell et al. 2005; Schott et al. 2007; Eppinger, Nystrom, and

Cohen 2012; Eppinger et al. 2013). However, Widmer et al. (2017) showed that the ventral striatum displayed stronger activation in elderly compared to younger adults when performing an arc-tracking task where feedback involved monetary reward, which might indicate altered processing of reward in elderly during a motor task.

An interesting observation was that a large part of the younger participants developed explicit knowledge of the context-force associations, which is in contrast to our study from Chapter 4 where a smaller percentage of older adults developed awareness of the relationship between context and direction of force. Cognitive decline has shown to increase with aging (Harada et al. 2013), which may possibly explain why a larger part of younger adults reported explicit awareness. Due to the small sample size of young adults and the counterbalancing of conditions within our task there was no valid opportunity to explore the differences in performance between those who gained explicit awareness and those we did not, but it is an interesting observation that hopefully will be explored by future research. Also, it has been shown that the degree of involvement of explicit processes during reinforcement learning crucial consequences has on performance during adaptation (Holland et al. 2018; Codol et al. 2018). If the involvement of explicit processes is influenced by aging this may lead to various performance on adaptation tasks in younger versus older adults as seems the case in our studies.

Altogether, our results show that enhancing reward, punishment, or both does not improve context-dependent force-field adaptation in young adults. However, small differences in adaptation between the groups were observed, which might indicate the presence of an effect of the success-based feedback. Especially since group differences

were found for peak velocity of movement during baseline and re-adaptation. A larger sample size could potentially help expose a similar effect on adaptation itself.

Chapter 6

General Discussion

6.1 Introduction

In this Chapter, I will summarise and discuss the main findings of my studies. I will expand on topics previously mentioned as well as introduce some new ideas derived from the preceding chapters. The aim of this thesis was to investigate motor memory deficits in PD and shed light on potential underlying mechanisms of the deficit. We chose to do this using force-field adaptation paradigms as this type of adaptation is unexplored in PD and offers new insights into how PD pathology affects motor learning. Our initial results led us to investigate motor adaptation further using a task where learning was dependent on the ability to link motor states to visuo-spatial contextual cues. We then also explored reinforcement of these associations using visual and auditory reward and punishment feedback. Our results indicated that PD pathology results in a weakened ability to establish context-motor associations, which might be caused by insensitivity to reward and/or punishment feedback, and may be underlying some of the motor memory deficits found by earlier studies.

6.2 Summary and discussion of results

In the first study we examined motor adaptation and motor memory in people with PD using force-field adaptation. Our results demonstrated both intact and impaired adaptation in people with PD. PD groups in experiment 2 showed incomplete error reduction, while the PD groups in experiment 1 showed adaptation similar to Controls. However, the PD groups in Experiment 1 also displayed a slightly larger LD at the end of adaptation indicating a similar but smaller difference compared to those from experiment 2.

Nonetheless, both PD groups showed substantial reduction in error at the beginning of the adaptation phases indicating adaptation. Therefore, we concluded that force-field adaptation in PD was largely intact, but slightly worse when compared to Controls. The reason for this impairment remains unclear, though adaptation is known to be a process mainly driven by the cerebellum, a brain area that is thought to be largely intact in PD, there may be alterations of the cerebellum in PD. These changes are believed to be both pathological (possible induced by abnormal signalling from the BG or due to dopaminergic degeneration or medication) and stemming from compensatory mechanisms and could be beneficial or detrimental on motor behaviour (Wu and Hallett 2013; Mirdamadi 2016). Knowledge regarding this topic is limited and further research needed to make these claims solid. However, we do not rule out that cerebellar defects were underlying the incomplete error reduction seen in our PD groups.

Another surprising finding was that people with PD exhibited intact recall, i.e. savings, of the learned force-field (similar as seen in healthy older controls), but had impaired interference. These findings are in contrast to earlier studies and raise further questions. Firstly, motor memory formation following force-field adaptation, as tested by savings, seemed largely preserved in our PD groups. Does this mean that the motor memory problems found by earlier studies were specific to the VMR task and do not apply to force-field adaptation (or dynamic adaptation in general)? Secondly, the fact that interference, but not savings, was severely affected in PD suggests that savings and interference are not two sides of the same coin, but instead must be – at least- partially separate processes. Could these results therefore indicate problems with retrieval of the

motor state in PD instead of problems with formation? However, if problems with motor memory retrieval are underlying some of the deficits in PD these problems should be provoked by specific (task) conditions, such that they would cause the impairments of both savings and interference when tested with VMR tasks, while only affecting interference when tested using force-field adaptation.

Interference has been studied by many, but only few examined interference in relation to its underlying mechanism. Motor learning in rodents has been shown to induce long-term potentiation (LTP) in the primary motor cortex (M1), which was then followed by a reduced ability to induce more LTP (Rioult-Pedotti, Friedman, and Donoghue 2000; Martin and Morris 2001) – an observation that possibly explains the phenomenon of interference. Such occlusion of LTP-like plasticity has also been shown in humans, using anodal TDCS (aTDCS) (Cantarero et al. 2013), and was correlated with an increase in anterograde interference. Induction of LTP seemed to recover over time both in rodents (Rioult-Pedotti, Donoghue, and Dunaevsky 2007) and in humans (Cantarero et al. 2013). The latter study also found a reduction of interference when more time was allowed between tests, which has also been shown by other studies (Shadmehr and Brashers-Krug 1997; Criscimagna-Hemminger and Shadmehr 2008). These results suggest that the reduced interference in our PD group could be related to an absence of LTP occlusion. A logical explanation for the lack of LTP occlusion, would be that LTP is not induced in the first place. Indeed, LTP has been shown to be affected in PD (Suppa et al. 2011; Kishore et al. 2012), which makes it plausible that deficits in LTP are underlying the

problems with motor memory in PD. However, our results indicate that other factors might also be at play.

Huang et al. (2011) suggested that interference occurs because during an A-B paradigm the same target, i.e. the same visual space, is associated with two different motor commands, i.e. two different movements in hand-space, leading to retrieval inhibition similar as seen for other paired-associative paradigms (Anderson, Bjork, and Bjork 2000; MacLeod and Macrae 2001). In line with this idea, Shadmehr & Holcomb (1999) had earlier shown that brain regions that were activated during adaptation to a force-field re-activated when a counter force-field was performed afterwards and proposed that the visual stimuli/context present during the task work as cues that reactivate the brain areas leading to interference. Similarly, savings of a visuomotor adaptation might be elicited by an explicit component, such as a cue or context, that could be acquired after only a few trials of adaptation (Huberdeau, Haith, and Krakauer 2015). Moreover, interference can be reduced when each field is linked to a different sensory contextual cue (Howard, Wolpert, and Franklin 2013). The fact that context is relevant during motor adaptation is very well displayed by studies where participants are asked to adapt to two opposing force-fields simultaneously, which is nearly impossible unless each field is associated with a context (Wada et al. 2003; Osu et al. 2004; Richter et al. 2004; Hirai et al. 2006; Hwang, Smith, and Shadmehr 2006; Addou, Krouchev, and Kalaska 2011; Baldeo and Henriques 2013; Howard, Wolpert, and Franklin 2013; Wang and Müsseler 2014; Ayala, Marius, and Henriques 2015; Yeo, Wolpert, and Franklin 2015). In addition, some studies have suggested that contextual processing impaired is in PD

(Fogelson, Fernandez-del-Olmo, and Santos-Garcia 2011; Li et al. 2018). If context-motor associations would be less strong in PD they would experience less interference during an A-B paradigm as memory of the first adapted state (A) would not be elicited when experiencing the opposite perturbation (B). Since we observed reduced interference in PD we hypothesized that people with PD were less able to form or maintain the link between a motor state and contextual cue.

In our second study we therefore investigated context-dependent motor adaptation in PD and found evidence that people with PD were less able to form context-force associations in comparison to healthy older Controls. When participants were tested for recall of the learned context-force association results were somewhat inconclusive as LD and FC showed both normal as well as weakened improvement of adaptation compared to Controls. However, figure 4.3 shows that the PD group starts re-adaption with positive FC values (instead of negative FC values as during Adapt 1) indicating increased anticipation of the force-fields. Altogether these results demonstrate that context-motor associations in PD may be less strong but were retained to some degree and used upon re-exposure.

In a second experiment the study was repeated, but feedback about success was enhanced by providing stronger reward and punishment feedback after trial completion (mainly using auditory stimuli). Earlier research on cognitive behaviour has shown operant reinforcement mechanisms to be affected in PD (Knowlton, Mangels, and Squire 1996; Frank, Seeberger, and O'Reilly 2004; Shohamy et al. 2005). It is likely that blunting of this mechanism in PD is also underlying the weaker context-force associations seen in

our PD group. However, we neither know if operant reinforcement mechanisms are responsible for learning context-force associations nor do we know if these mechanisms are affected in PD with regard to motor learning in general. With our second experiment we aimed at clarifying two things. The first being that reward and punishment during adaptation facilitate reinforcement of the context-force associations. And secondly, that if PD pathology leads to reduced sensitivity to reward and punishment PD participants would be less able to modulate their performance in response to the enhanced feedback.

Our hypothesis was that providing stronger reward and punishment through auditory feedback would activate operant reinforcement mechanisms in older Controls, but not in PDs, to a higher degree therefore leading to improved performance on the contextual motor task. Our hypothesis was proven correct with respect to the visual error, i.e. lateral deviation declined more quickly, and force compensation, as both LD and FC revealed a significant difference between the PD and Control group. In addition, the PD group did not display improvements in response to augmented feedback, therefore suggesting reduced sensitivity to reward and punishment. These results imply that operant reinforcement mechanisms were impaired for motor learning just as seen for cognitive behaviour. Interestingly though, similar to the Control group the PD group showed after-effects when the force-fields were removed, while an after-effect was not observed during experiment 1 (no enhanced feedback) in both groups. So while reward and punishment did not improve acquisition of the context-force associations in the PD group, it did increase retention of the learned associations.

Normally the presence of retention is associated with a change in the internal model, which can be measured by the presence of an after-effect (Shadmehr and Mussa-Ivaldi 1994). The lack of after-effects in the PD and Control group in experiment 1 may imply that the internal forward model was not updated. Previous studies have shown that when adaptation involves explicit processes, such as when participants use a cognitive strategy to compensate for the perturbation, aftereffects are reduced (Benson, Anguera, and Seidler 2011; Taylor and Ivry 2011). Therefore, our results from experiment 1 may suggest that contextual motor adaptation was mainly driven by explicit rather than implicit processes. It must be noted that a 30-minute break passed before after-effects were tested so some retention might have been present, but could have decayed in the 30-minute time window. Experiment 2 did show significant retention, therefore implying that reward and/or punishment improved formation of an internal model of the context-force association; possibly through increased involvement of implicit processes. While it remains questionable what processes exactly are involved in contextual motor learning, our results might imply a higher involvement of cognitive processes during context-dependent motor adaptation in the absence of explicit extrinsic reward and punishment.

A recent study has suggested that reward and punishment have dissociable effects on adaptation and retention (Galea et al. 2015); punishment enhancing adaptation, whereas reward improves retention. It has also been shown that people with PD ON medication - as our PD participants - sensitive are to positive and not negative outcomes, while an OFF state of medication reverses this phenomenon (M. J. Frank, Seeberger, and O'Reilly 2004). The observation that our PD group improved retention, but not adaptation

of the context-force associations could indicate that the dissociable effect of reward and punishment as proposed by Galea et al. (2015) also holds for context-dependent force-field adaptation.

In a third study (Chapter 5) the separate effects of reward and punishment on contextual motor adaptation were investigated using a cohort of younger adults. With this study we hoped to provide better insight into the separate contributions of reward and punishment feedback on adaptation, retention, and recall of associations involving context-motor relationships. Although no significant effects were found on LD reduction or force compensation, the study revealed slight differences, which may indicate that the various forms of feedback had some effect. The Control group (no enhanced feedback) showed the worst performance, while the group that received augmented punishment showed the best performance. Assessment of peak velocities did reveal a significant benefit of additional feedback during baseline and increased peak velocity of the Punishment group during re-adaptation therefore showing that the different forms of feedback had an effect on some aspects of performance. While increased peak velocity during baseline could suggest motivational benefits caused by the augmented feedback, the improvement of the Punishment group during re-adaptation implies a lasting effect of the feedback received during Adapt 1, especially since feedback was similar between all groups during re-adaptation.

Although the younger adults receiving both enhanced reward and punishment showed a slight improvement in LD reduction compared to the younger controls who did not receive enhanced feedback, no group differences were found. Older adults have

shown to perform worse on adaptation tasks (Panouillères et al. 2015; Hardwick and Celnik 2014), but our results suggest they performed similar to (or even better than) younger adults; Older Controls [Ch4 – Exp 1] - early A1 [block 21]: 1.3 ± 0.2 cm, late A1 [block 60]: 0.7 ± 0.2 cm; Young Controls - early A1: 1.5 ± 0.1 cm, late A1: 0.9 ± 0.1 cm). Though, in contrast, younger adults from the Control group showed retention, while the older adults failed to show retention when not provided with enhanced feedback. Our results might therefore indicate that younger adults rely less on extrinsic reward and punishment to retain context-motor states. Dopamine levels decline with aging leading to incomplete RPE signals (Chowdhury et al. 2013), which could lead to older adults having to rely on alternative processes. Altogether, while our results could indicate that older adults might rely more on extrinsic reward signals to activate reinforcement mechanisms, whereas younger adults could be less dependent on such feedback further research is needed including direct comparisons between older and younger adults and using larger sample sizes.

6.3 Medication

Participants with PD remained on their medication during our studies. Dopamine, which is involved in the signalling of reward and punishment through peaks and dips in dopamine, is partly replenished by dopaminergic medication. Earlier work has suggested that dopaminergic medication can influence performance on a cognitive procedural learning task by altering sensitivity to positive and negative outcomes (M. J. Frank, Seeberger, and O'Reilly 2004; Michael J Frank 2005). This dissociation in sensitivity

seems to be caused by an OFF state leading to difficulties with generating dopamine peaks, while an ON state makes it harder to generate dopamine dips, due to altered baseline levels of dopamine. Adaptation seems not be affected by medication as Mongeon, Blanchet, and Messier (2013) directly compared adaptation between people with PD ON and OFF state and showed that medicated state had no effect on implicit adaptation (also see discussion section 3.4). In contrast, their study showed that explicit adaptation was diminished in both PD groups compared to Controls suggesting that PD pathology has a larger effect on explicit, rather than implicit, processes involved in adaptation irrespective of medicated state. These findings contribute to earlier research showing that implicit adaptation is driven by the cerebellum, which is relatively unimpaired in PD.

Motor memory following adaptation has shown to be affected in PDs ON (Marinelli et al. 2009; Bédard and Sanes 2011; L. A. Leow, Loftus, and Hammond 2012; L.-A. Leow et al. 2013) and OFF state (Krebs et al. 2001; Marinelli et al. 2009). Our PD groups ON medication showed impaired motor memory only by reduced interference, but not savings. Motor memory retrieval following adaptation is thought to be facilitated by the BG, rather than the cerebellum. In theory, the deficits in motor memory might be more present in those OFF meds as reward-based signalling is more highly affected when people with PD abstain from dopaminergic treatment (Michael J Frank 2005).

Studies on habit formation show a deficit in learning S-R associations in PDs ON medication (Saint-cyr, Taylor, and Lang 1988; Knowlton, Mangels, and Squire 1996; Ashby et al. 2003). Similarly, we found impaired context-dependent force-field learning

while testing PD participants ON mediation. Nonetheless, these deficits might be even more so present in those OFF medication (Frank 2005; Shohamy et al. 2005). However, in order to make a clear conclusion about the effects of medication on (contextual) motor learning and reward-based feedback in PD studies are needed where people with PD are tested both ON and OFF state.

6.4 Limitations & Future Directions

Chapter 4 investigated the effect of success-based feedback on contextual motor learning in PDs and Controls by adding reward and punishment feedback (visual and/or auditory stimuli) to the initial experimental conditions (Exp 1). Similarly, in Chapter 5 a Control-group was used with task conditions similar to those used in Chapter 4 – Exp 1, as comparison to three other groups with additional reward and/or punishment feedback. It must however be noted that the control-condition also included binary information about success, namely a change of color of the target (red/yellow), which is a form of success-based feedback. Although the different task conditions still allowed investigation of the relative effects of reward/punishment feedback, the inclusion of some success-based feedback in the control group might have blunted the results. Stronger effects of success-based feedback might have been shown if only visual error was used as a control group. In future studies we intend to include a control group without binary information about success.

Following our results it remains somewhat unclear whether PD pathology affected motor learning through deficits in contextual learning, reward-based learning or both. An

assessment of operant reinforcement in a motor task without context, and vice versa, an investigation of contextual motor learning without success-based feedback, might make it possible to differentiate better between the two. However, even in the absence of its explicit presence a contribution may still be made. Some studies presented in this thesis might also have suffered from a low sample size. In Chapter 4, a power analysis on experiment 1 showed that there was not sufficient power, which may have prevented us from finding a statistical group difference in performance. Similarly, low sample sizes might have blunted the beneficial effect of enhanced success-based feedback on performance in Controls. Overall, some of the results presented in this thesis made it hard to adopt clear conclusions, as they were contradictory or inconclusive. The sample sizes used as well as the experimental design might have contributed to these limitations.

The investigation of reward and punishment in motor learning has gained more attention and popularity over the years. Context-dependent motor learning, on the other hand, is still a relatively unexplored field, but earlier studies have displayed the importance of contextual cues during motor learning. Both contextual cues and success-based information seem important neuromodulators that, via the BG, help shape motor learning and motor memory. We believe that motor adaptation studies should pay more attention to contextual information present during adaptation, both in terms of its separate effect as well as in combination with success-based information.

Some of the findings presented in this thesis ask for further investigation. For instance, future motor studies might want to focus on the separate effects of reward and punishment feedback on those affected with PD pathology as well as how findings relate

to non-lab settings, such as rehabilitation therapy. Future studies might also want to pay more attention to the explicit processes involved during context-dependent motor learning as we observed that some participants gained explicit awareness during the task. The contribution of explicit processes might differ depending on age or PD pathology. To determine the effect of aging on context-dependent/success-based motor learning a study is required where a direct comparison can be done between groups of different ages.

6.5 Conclusion

We provided evidence that a diminished ability to create neurobiological links between contextual cues and motor states might be underlying some of the motor memory problems seen in PD. In addition, our results suggest that a defective operant reinforcement system might be responsible for the weakened associations, as PD participants were unable to strengthen the context-force associations in response to augmented reward and punishment. It remains inconclusive how reward and punishment exactly affect context-dependent force-field adaptation, retention and recall, but older adults might benefit from augmentation of reward and punishment when learning context-force associations. This insight offers possible applications with respect to the elderly population, such as rehabilitation from injuries or learning assistance, but needs further investigation in non-lab settings. While the results found provide insight into how PD pathology affects motor adaptation and motor memory, in particular how it affects force-field learning and the importance of context, more experimental work is needed to answer

remaining questions and provide more detailed insight into the mechanisms underlying motor memory.

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Appendix I – Supplementary figures Chapter 3, 4, and 5

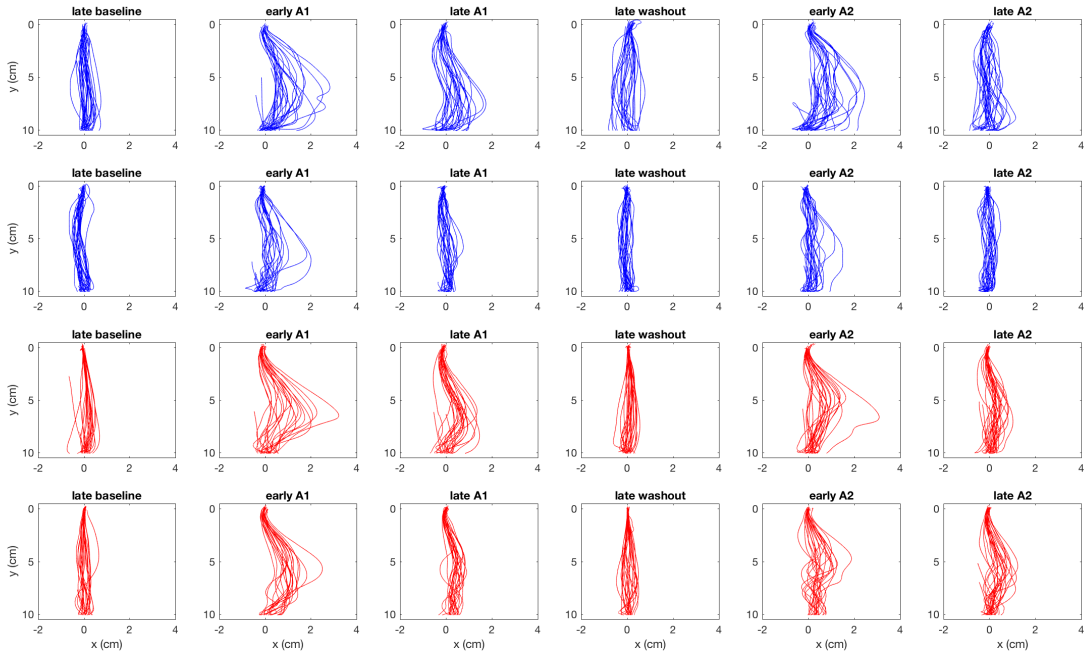

Figure S1. Chapter 3 - Individual trajectories of two PD subjects (blue, two top rows) and two Control subjects (red, two bottom rows) of the savings condition of experiment 1 (1-hour break). Trajectories are shown in batches of 20 trials for baseline (last 20 trials), the first adaptation phase (A1; first 20 trials), late A1 (last 20 trials), washout (last 20 trials), early and late A2 (first and last 20 trials).

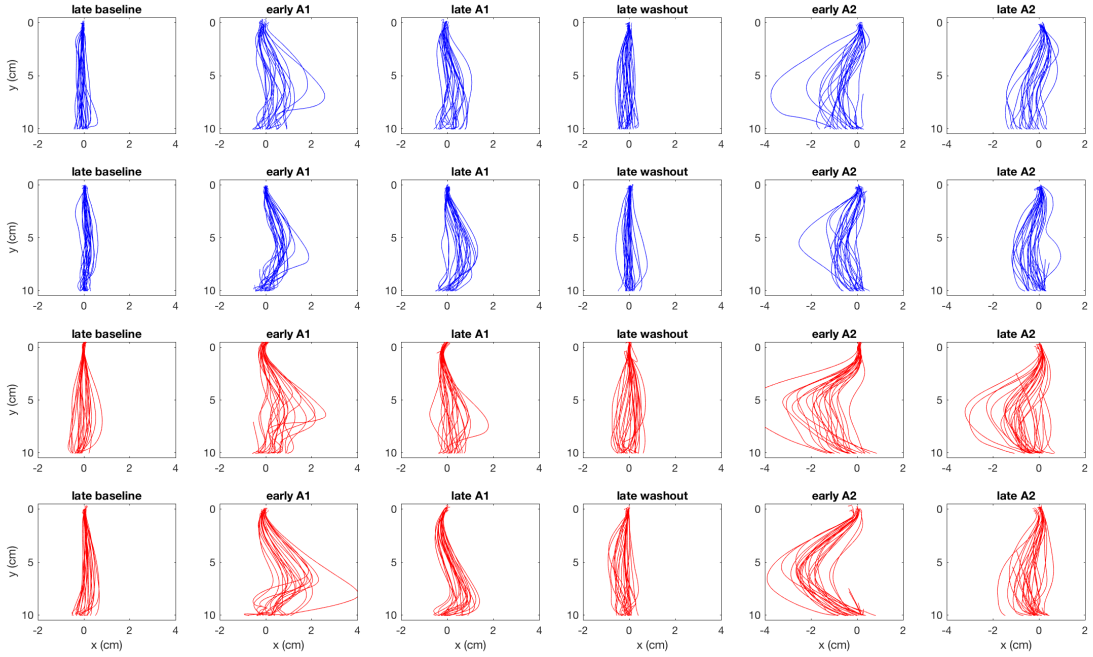

Figure S2. Chapter 3 - Individual trajectories of two PD subjects (blue, two top rows) and two Control subjects (red, two bottom rows) of the interference condition of experiment 1 (1-hour break). Trajectories are shown in batches of 20 trials for baseline (last 20 trials), the first adaptation phase (A1; first 20 trials), late A1 (last 20 trials), washout (last 20 trials), early and late A2 (first and last 20 trials).

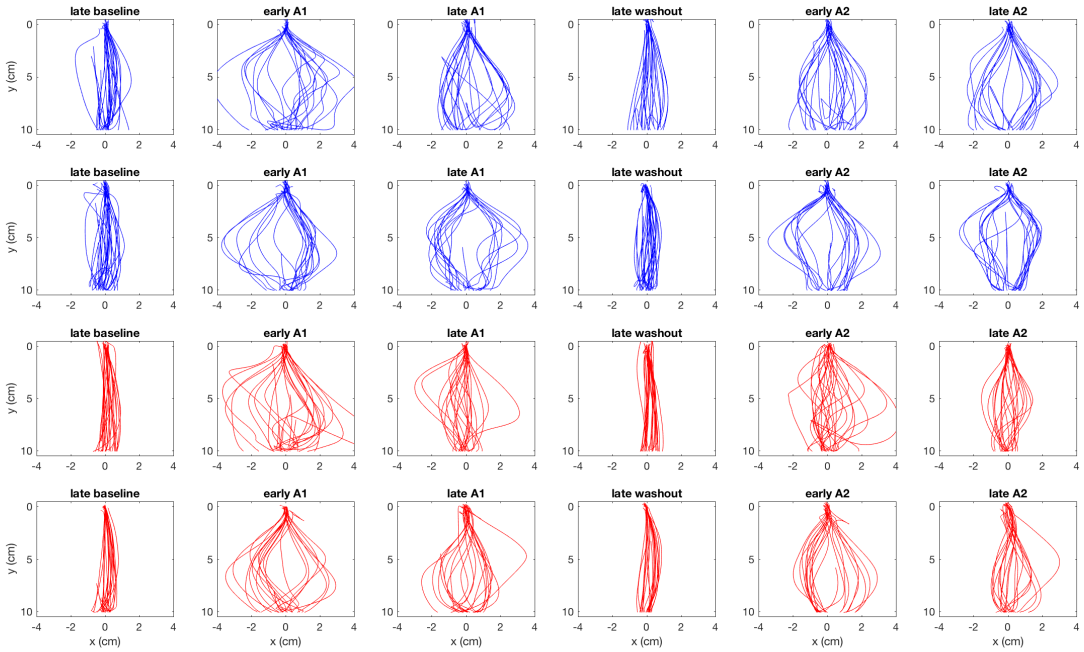

Figure S3. Chapter 4 - Individual trajectories of two PD subjects (blue, two top rows) and two Control subjects (red, two bottom rows) of the context-dependent task (experiment 1). Trajectories are shown in batches of 20 trials for baseline (last 20 trials), the first adaptation phase (A1; first 20 trials), late A1 (last 20 trials), washout (last 20 trials), early and late A2 (first and last 20 trials).

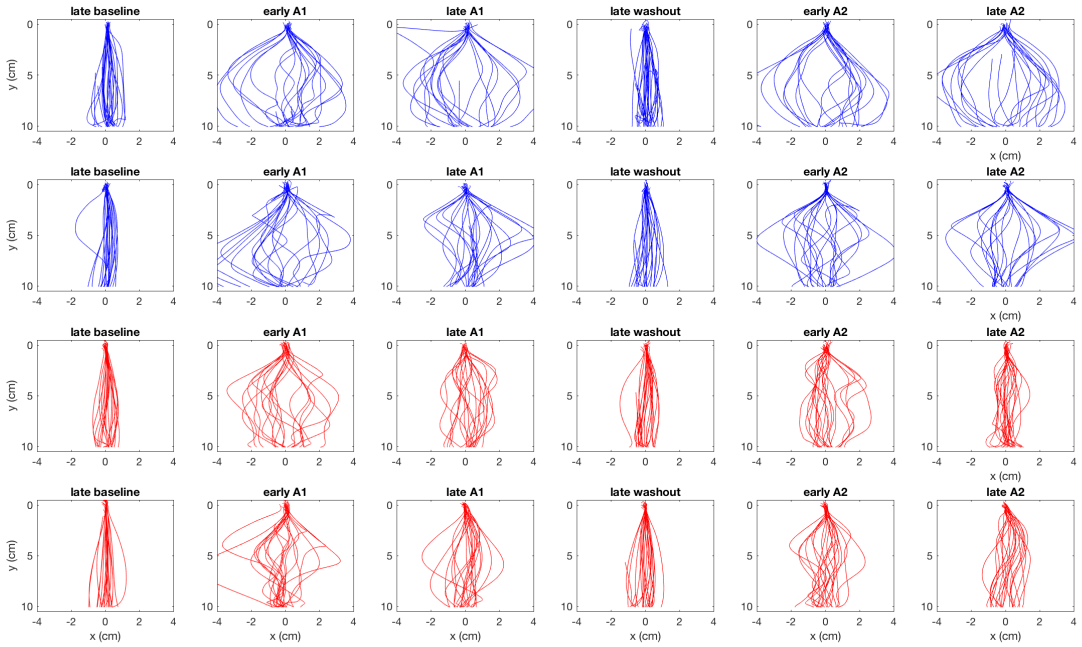

Figure S4. Chapter 4 - Individual trajectories of two PD subjects (blue, two top rows) and two Control subjects (red, two bottom rows) of the context-dependent task with enhanced reward/punishment feedback (experiment 2). Trajectories are shown in batches of 20 trials for baseline (last 20 trials), the first adaptation phase (A1; first 20 trials), late A1 (last 20 trials), washout (last 20 trials), early and late A2 (first and last 20 trials).

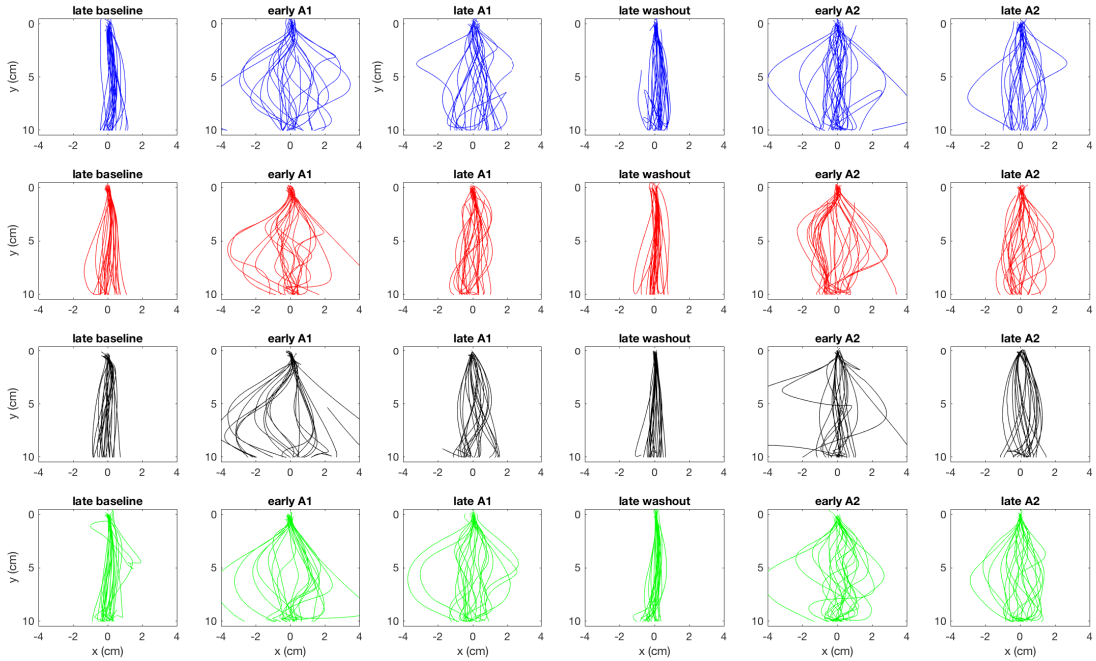

Figure S5. Chapter 5 - Individual trajectories of a subject from the Control group (blue), R&P group (red), Punishment group (black), and the Reward group (green) during the context-dependent motor task. Trajectories are shown in batches of 20 trials for baseline (last 20 trials), the first adaptation phase (A1; first 20 trials), late A1 (last 20 trials), washout (last 20 trials), early and late A2 (first and last 20 trials).

Appendix II – Medication Chapter 3 and Chapter 4

Table 3.2 Medication details PD participants – Chapter 3

	Experiment 1		Experiment 2	
	Savings (N = 12)	**Interference** (N = 12)	**Savings** (N = 11)	**Interference** (N = 12)
Levodopa	8	10	10	9
Dose (mg)	350 ± 53	465 ± 49	460 ± 74	461 ± 40
DA receptor agonist	8	9	5	8
MAO-B inhibitor	5	5	3	5

Table 4.1 Medication PD group Experiment 1 - Chapter 4

	PD participants (N = 10)
Levodopa	8
Dose (mg)	469 ± 89
DA receptor agonist	5
MAO-B inhibitor	1

Table 4.2 Medication PD group Experiment 2 - Chapter 4

	PD participants (N = 10)
Levodopa	8
Dose (mg)	409 ± 45
DA receptor agonist	6
MAO-B inhibitor	6